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THE EFFECT OF CHEMICAL PRODUCTS OF MUSCULAR ACTIVITY ON THE FREQUENCY AND FORCE OF THE HEART BEAT

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Introduction

INTEREST in the possible role of products of muscular activity in the cardiac acceleration due to muscular exercise began with the experiments of Mosso,[1] in which an increase of heart rate was produced in the resting animal (dog) by the injection of blood from an animal fatigued by muscular exercise. Investigators since this time have attacked this problem by a number of different methods, and their studies have led to the advancement of several different explanations of the increase in heart rate as a result of activity of the skeletal muscles. So far as we have been able to find, such studies have been confined to experiments in the intact animal with the heart *in situ*, a condition which, in the light of recent work, makes it difficult to determine whether the effects observed are to be interpreted as a direct action on the heart, or result from indirect action on this organ through the intervention of some other mechanism of the body. Thus v. Anrep[2] has recently shown that the pressor action of products formed during asphyxia is in part due to stimulation of the adrenal glands. Experiments in which the action of fatigue products has been tested

on the heart *in situ* have been made by Johansson [3] and by Athanasiu and Carvallo.[4] These investigators observed the effect on heart rate of tetanization of the distal end of the sectioned spinal cord. In both series of experiments a slight acceleration of the heart occurred under these circumstances which persisted after section of the extrinsic cardiac nerves. The conclusion was, therefore, that there is some direct action of the products of metabolism on the heart independent of its extrinsic nerves, and that this action plays a role in cardiac acceleration in muscular exercise. This conclusion has been denied by Mansfeld,[5] who found that the effect described by Johansson and by Athanasiu and Carvallo is absent when means are used to prevent the blood which passes through the heart during the period of tetanization having a higher temperature than normally. He obtained negative results also from extracts of active muscles and from blood of fatigued animals when the influences due to change of temperature were controlled.

The demonstration by Geppert and Zuntz,[6] that the respiratory rate may be increased by metabolic products, has been a further stimulus to the study of the possible role that these play in cardiac acceleration. Certain substances known to be increased during muscular activity have been separately tested on the isolated mammalian heart perfused with saline solution, but the results from these researches would seem to furnish little evidence in reference to the effect of metabolic substances present in combination in the tissues or blood of the intact animal. The specific action of single products of metabolism has been found in certain cases to be antagonistic.[1]

In view of the contradictory results stated above, and in the absence of experimental results concerning the possible direct action of the combined metabolic products formed by the active muscles on the heart when indirect factors are excluded, we were led to

[1] Carbon dioxide was found by Jerusalem and Starling [7] and Ketcham, King and Hooker [8] to cause a slowing of the isolated mammalian heart. Bachmann [9] investigated the action of various nitrogenous extractions in Göthlin's solution on the isolated rabbit's heart. Sodium lactate in small quantities depresses; in larger amounts, equal to that which occurs in the blood after excessive muscular activity, acceleration was produced. Creatin in certain strengths increased the size of beat, but was without influence on the rate.

undertake the experimental work reported in this paper. We have employed the isolated and artificially perfused heart in all experiments, since it is only under these conditions that possible influences due to temperature changes, variations in blood pressure, or to indirect effects through other organs are excluded.

Method and Description of Experiments

In this series of experiments, six cats' hearts were perfused by Langendorff's method, using Locke's solution containing defibrinated cats' blood. The apparatus used for perfusion was that recently described by Eyster and Loevenhart,[10] in which the temperature of perfusion is controlled within narrow limits and in which a rapid change from one perfusion solution to another may be made. The hearts were rapidly removed and suspended in the apparatus immediately after free bleeding from the carotid under light ether anesthesia. Record of the rate and size of beat of the ventricles was obtained by direct connection of the apex of the left ventricle with a recording lever. Muscle extracts were made from resting or tetanized cats' muscles as follows: 200 gm. of thigh muscle was passed through a grinding machine and received in 200 cc. of 0.9 % NaCl at 37° C. This was placed in a shaking machine for four hours, the temperature being kept approximately constant, and then filtered through cotton wool. From 25 to 100 cc. of extracts made in this way were added to 4 litres of Locke's solution containing defibrinated blood from a cat which had not been subjected to stimulation. The first experiment served as a control to determine any possible influence of the extract of resting muscle. Experiments in which the effect of extracts from tetanized muscle was studied (III and IV) were further controlled by similar extracts from resting muscle previously perfused through the same heart. Since it was desirable to employ in these experiments hearts from animals which had been anesthetized lightly and for a short period of time, and also to have fresh extracts or blood for perfusion, two or more animals were used for each experiment. Fatigued muscle for extraction was obtained by anesthetizing an animal with ether, cutting the spinal cord in the lumbar region, and stimulating the distal end with a faradic current for periods of from three quarters

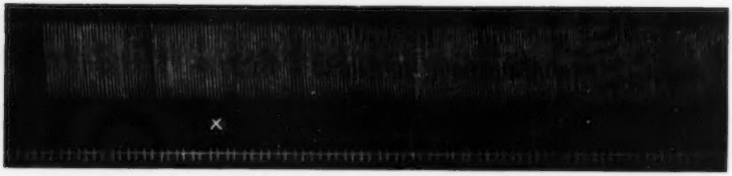

FIGURE 1. Experiment I. Shows the absence of effect on rate or size of beat from changing from normal perfusion to a perfusion solution containing extract of resting muscle (1 cc. of extract to 40 cc. Locke's solution containing defibrinated blood). In this and succeeding figures the lower line marks the time in intervals of one second. The upper line is a suspension curve of the ventricles, the upstroke of which represents systole. All records read from left to right. The mark X indicates the change from normal perfusion to perfusion with the extract.

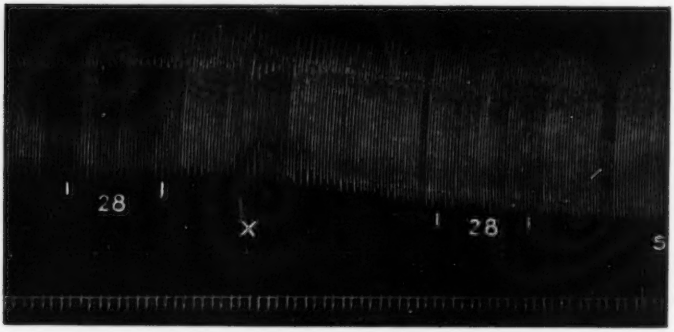

FIGURE 4A. Experiment IV. Increase of size of beat as a result of perfusion with blood from tetanized animal. The change to fatigue blood was made at X. The increase in size of contraction is mainly due to increased relaxation in diastole.

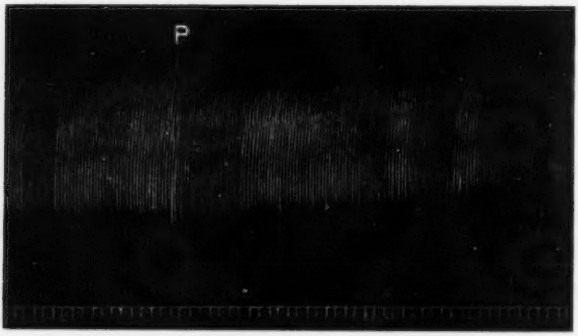

FIGURE 4B. Shows return to normal after the period of perfusion shown in 4a. The size of the beat is reduced and diastolic tone is rapidly regained.

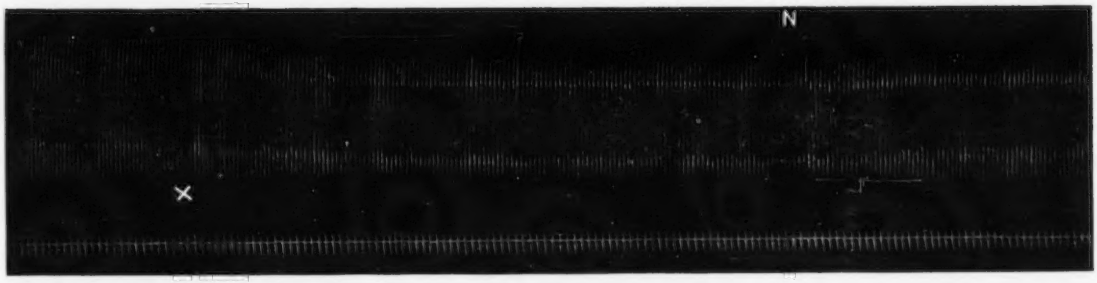

FIGURE 2. Experiment II. Shows the diminished beat as a result of perfusion with a strong extract (1 cc. to 40 cc. of Locke's-blood solution) of fatigued muscle. At the mark X change was made from the normal perfusion to perfusion with the extract. At N return was made to normal perfusion. The effect is mainly on the height of systole.

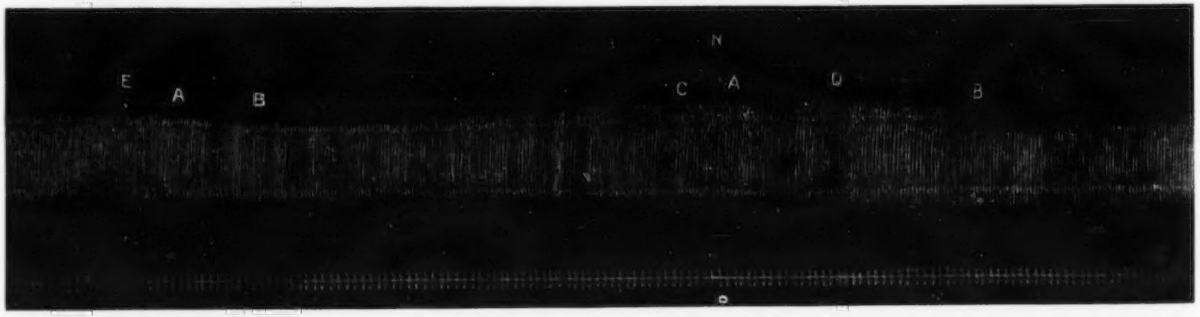

FIGURE 3. Experiment IV. Shows increase of size of beat as a result of perfusion with weaker extract (1 cc. to 160 cc. of Locke's-blood solution) of fatigued muscle. Change from normal perfusion to perfusion with extract was made at E, return to normal at N. The increase affects mainly systole, and in this case is preceded by transitory and slight decrease in size of beat.

to one and a half hours. Stimulation was stopped only when fatigue was sufficient to render the muscle no longer irritable to such stimulation. The thigh muscles were then quickly removed and extracted by the method described above. In one experiment (II) the whole limb was ligated except the nerve, in the others the normal blood flow was maintained in the limb throughout the period of tetanization. In two experiments (V and VI) the blood of the tetanized animal was employed instead of the extract from the muscle. Further points in reference to the details of the experiments will be found in the protocols.

Results

An extract from the resting cat muscle, made in the manner described above and used in a strength of 1 cc. of the extract to 40 cc. of the perfusion solution, was without effect on the isolated cat's heart. A corresponding strength of extract from muscle that had been tetanized under the conditions described above produced a slight decrease in size of beat, manifested as a diminution in extent of contraction, with no definite change in rate. Extracts from tetanized muscle of one-half and one-fourth this strength (Exps. III and IV) caused an increase in the size of beat. In the stronger solution this increase was transitory and was followed by a decrease. The increase usually affected both systole and diastole, resulting in an augmented height of contraction and an augmented relaxation in diastole (diminished diastolic tone). In other cases only the extent of systole was affected. The rate in each case was slightly reduced during perfusion with a solution containing the extract from tetanized muscle. Blood from a tetanized animal, when added to the perfusion fluid, produced a change similar to that caused by the weaker mixtures of extract; namely, a moderate increase in size of beat with no change or a slight decrease in rate. The increase was mainly and, in some cases, entirely the result of increased diastolic relaxation. Increased perfusion through the coronary arteries was present in Experiment IV during the period of increased contraction of the heart. Figures 1 to 4 give examples to illustrate the above statements.

Conclusion

Metabolic products, formed in active muscles, play no part in the increase in heart rate resulting from muscular activity, in so far as this action is upon the heart muscle directly or upon the cardiac endings of the extrinsic nerves. It seems probable, however, that such action may play a part in the increase in size of the heart beat observed under these circumstances.

Protocols

Experiment I. Control experiment to determine effects, if any, of extract from resting cat's muscle on isolated cat's heart. Cat anesthetized lightly with ether and killed by bleeding from carotid. 200 gm. of thigh muscle ground and extracted with 200 cc. NaCl at 37° C. in shaking machine for four hours. A second cat was then etherized and bled from carotid, blood defibrinated and added to the perfusion solutions. The heart from this cat was suspended in the apparatus and perfusion begun. The perfusion solutions employed were made up as follows:

Solution I. 4100 cc. Locke's solution, 65 cc. resting cat's blood.

Solution II. 4000 cc. Locke's solution, 65 cc. resting cat's blood, 100 cc. extract of resting muscle.

The temperature of perfusion throughout the experiment was 35.5, C.° the pressure 48 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.	Outflow in ccm. in 30 sec.
Normal (I)	60	15.0	11.5
	60	15.0	11.5
Extract (II)	59	15.0	11.0
	59	14.0	11.0
Normal (I)	57	14.0	11.0
	57	14.0	10.0
Extract (II)	58	13.5	10.5
	58	13.0	10.0

Experiment II. Effect of extract from tetanized cat's muscle with circulation cut off on isolated cat's heart.

First cat anesthetized, spinal cord exposed and cut. One posterior limb ligated with exception of sciatic nerve, and distal end stimulated for one hour with faradic current, the animal being kept alive and anesthetized during this period. Extract made from muscles of this leg by the usual procedure. Second cat was now anesthetized, bled from carotids, blood defibrinated, and heart suspended. The perfusion solutions used were made up as follows:

Solution I. 4100 cc. Locke's solution, 35 cc. resting cat's blood.

Solution II. 4000 cc. Locke's solution, 35 cc. resting cat's blood, 100 cc. extract of tetanized muscle.

Temperature of perfusion 35.5° C. Pressure 50 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.
Solution I (Normal)	50	22.0
Solution II (Extract) ...	47	22.0
	47	17.0
Normal (I)	47	17.0
	47	18.5
Extract (II)	44	18.0
	42	13.0
Normal (I)	42	19.0
Extract (II)	41	19.0
	41	15.5
Normal (I)	39	15.5
	39	19.0
Extract (II)	39	19.0
	39	16.0
Normal (I)	38	16.0
	38	17.0
Extract (II)	38	17.0
	38	13.0

Experiment III. Action of more dilute extract of tetanized muscle, in which the normal blood flow was maintained throughout the period of tetanization, compared with extract of resting muscle on the isolated cat's heart. First cat anesthetized, cord exposed, cut, and stimulated for forty-five minutes. Thigh muscles removed and placed in shaking machine along with an extract of resting muscle obtained from a second cat, which was anesthetized and bled to death. These were kept in the shaking machine for four hours, and at the end of this time a third cat was anesthetized, bled, and heart suspended. The solutions were made up as follows:

Solution I. 4000 cc. Locke's solution, 35 cc. blood of resting cat, 50 cc. extract of resting muscle.

Solution II. 4000 cc. Locke's solution, 35 cc. blood of resting cat, 50 cc. extract of blood from tetanized muscle.

Temperature of perfusion 35.5° C. Pressure 47 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.
Solution I (Normal) ...	67	13.5
Solution II (Tetanized).	65	13.0
	66	15.0
Normal (I)	66	15.0
	66	15.0
Tetanized (II)	64	16.5
	63	18.0
Normal (I)	62	17.0
	63	16.5
Tetanized (II)	62	17.5
	59	16.0
Normal (I)	57	16.0
	52	13.5

Experiment IV. This experiment was an exact duplication of Experiment III, except that the extract of resting and fatigued muscles were of

still lower strength: 1 cc. of the extract to 160 cc. of the Locke's blood perfusion solution. The muscles from which the fatigue extract was made were tetanized for one hour. The two perfusion solutions were made up as follows:

Solution I. 4000 cc. Locke's solution, 27 cc. blood of resting cat, 25 cc. extract of resting muscle.

Solution II. 4000 cc. Locke's solution, 27 cc. blood of resting cat, 25 cc. extract of tetanized muscle.

Temperature of perfusion 35.5° C. Pressure 56 mm. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.	Outflow in ccm. in 30 sec.
Solution I (Normal) ...	80	18.5	
Solution II (Tetanized).	75	18.0	
	72	23.5	27.0
	68	32.5	
Normal (I)	65	32.5	
	63	29.0	17.0
	63	28.0	16.0
Tetanized (II)	63	28.0	
	63	31.5	19.5
	62	31.5	20.0
Normal (I)	62	31.5	
	59	29.0	16.0
	62	26.5	15.0

Experiment V. Effect of blood from tetanized animal on the isolated heart. First cat was anesthetized, spinal cord cut, and distal end stimulated for one and one-half hours. The animal was then bled, the blood defibrinated and added to Locke's solution. A second cat was then anesthetized, bled, and the blood defibrinated and added in same amounts to the control solution. The heart from this cat was suspended and the two solutions tested. The solutions were made up as follows:

Solution I. 3000 cc. Locke's solution, 37½ cc. blood from resting cat.

Solution II. 3000 cc. Locke's solution, 37½ cc. blood from cat in which muscles of posterior limbs had been tetanized for one and one-half hours.

Temperature of perfusion 35.5° C. Pressure 50 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.
Solution I (Normal) ...	102	14.0
Solution II (Tetanized) .	99	14.0
	98	17.0
	96	19.0
Normal (I)	95	18.5
	99	17.5
	93	17.0
Tetanized (II)	92	18.5
	91	21.5
	89	20.0

Experiment VI. This experiment was identical with the preceding in procedure and results. The cord was stimulated in the tetanized animal for one hour and forty minutes and 50 cc. of blood from each animal was employed.

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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

XI. The Cause of the Polyphagia in Pancreatic Diabetes

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ONE of the striking symptoms of the diabetes mellitus induced in dogs by the complete removal of the pancreas is the voracity which these animals exhibit, especially during the terminal stages of the disease. Reduced to mere skeletons of their former selves by a rapid and progressive emaciation, their dry skin bearing indolent ulcers resulting from slight scratches, with eyes almost closed with a purulent conjunctival discharge, such animals will eat ravenously. In this extreme cachetic condition which precedes their death, when they are entirely indifferent to their surroundings and lie in their cages almost too weak to rise, they will liven up at the sight and smell of food and will muster up all their strength in an endeavor to get at the food and devour it. It is, therefore, not uncommon to find their stomachs at autopsy filled with food ingested but a few hours previously. Such dogs have been known to eat their own feces even when provided with food which for a normal animal would be an abundant day's ration.

A similar polyphagia has been described in man as occurring occasionally during the course of diabetes mellitus or marasmus arising from other causes. In a recent article on diabetes in early infancy Knox[1] mentions hunger among the more common symptoms of the disease.

An animal, however, exhibiting a comparable decrepid condition but of different etiology (pneumonia, parathyroid tetany, distemper), would certainly refuse food.

Does, then, an animal dying from pancreatic diabetes eat because it is *hungry?* Or does this polyphagia result from some

[1] Knox: Bull. Johns Hopkins Hospital, Sept., xxiv, No. 271, 1913.

perverted appetite induced by the diabetic condition? In other words, is the voracity a result of true hunger pains brought on by real hunger contractions?

Methods

Two female dogs were used. The modified Frank's gastrostomy described in a previous paper [1] provided fistulous openings for the insertion of the rubber balloon recording changes in the intragastric pressure. The records of the movements of the empty stomach (hunger contractions) were taken as previously reported. After taking daily records of the movement of the empty stomach in the normal animal the entire pancreas (Dog I) or the pancreatic graft (Dog II) was removed and daily records again taken from the empty stomach while the animal was succumbing to the effects produced by the complete pancreatectomy.

Results

Dog I. Small fox terrier. Gastrostomy Nov. 6, 1912. Uneventful recovery. Contractions of the empty stomach exhibited the type described recently as type I.

Dog I. Figure 1. Nov. 28, 1912. About two-thirds the original size. Type I contractions—the type of contraction characteristic for this animal before the onset of pancreatic diabetes. Horizontal line represents 0 mm. bromoform pressure.

On Nov. 23, 1912, supposedly complete pancreatectomy.

On Nov. 27, 1912, the animal had recovered from the effects of this severe operation. The hunger contractions conformed to the type

[1] Carlson: this Journal, 1913, vol. xxxii, p. 369.

described as type I and there was no change during the succeeding days (Nov. 28–30 inclusive). Figure 1 — An examination of the urine revealed the absence of sugar. The animal was, therefore,

Dog I. Figure 2. Jan. 7, 1913. About two-thirds the original size. Character of the stomach contractions after pancreatic diabetes was well established; type II and III contractions superimposed on periods of marked tetany. Plain horizontal line represents o mm. bromoform pressure.

used for the study of another problem until the Christmas holidays. On Jan. 4, 1913, it was noticed that the dog ate ravenously, but was in an extremely emaciated condition. The skin was dry; the dog had the mange; there were multiple small wounds about the toes and ears; and a purulent discharge issued from both eyes. The urine reduced Fehling's (2.49%) and fermented readily with

Dog I. Figure 3. Jan. 24, 1913. About four-sevenths the original size. Well marked type III contractions of the empty stomach. The horizontal line represents o mm. bromoform pressure.

yeast. From Jan. 6, 1913, on, daily tracings were taken from the stomach 24 hours after the last meal.

On Jan. 6, 7, and 11, type III contractions predominated, super-

imposed on periods of tetany lasting from 1 to 7 minutes (Fig. 2). From the 11th of January on, type III was the most prominent type of contraction, with occasional reversion to type II. On the 18th, 21st, and 24th of January the stomach was in tetany, with type III contractions most pronounced (Fig. 3). On these days the dog ate a good deal of lean meat, as is seen from the following table:

TABLE I

Date 1913	Body weight in kg.	Food in gm.	Food in gm. per kg. body weight
Jan. 6	5.600	350	62.5
Jan. 7	5.400	313	48.9
Jan. 12		345	61.6
Jan. 14	4.800	429	89.3
Jan. 15		460	95.8
Jan. 18	4.400	400	90.9
Jan. 24		248	56.3
Jan. 25	4.000	140	35.0
Average	4.84		67.5

Jan. 25, 1913: Animal in a moribund condition. Rectal temperature 92.5° F. The dog was cold to touch. Could not stand unsupported. There were no marked movements of the stomach. The contractions were chiefly of type I variety. They were neither vigorous nor regular but nevertheless indicated slight hunger. At the end of the experiment the dog ate, with considerable difficulty, 140 gm. of lean meat. Immediate etherization. Stomach contained food just ingested. No macroscopic remnants of pancreas found. The 5 cc. urine found in the bladder did not reduce Fehling's solution.

The increased amount of food consumed by the animal towards the terminal stages of the disease (as high as 95.8 gm. meat per kg. body weight) compares favorably with a change in character and increased vigor of the hunger contractions.

Dog II. Fox terrier. Jan. 22, 1913: Pancreatectomy with pancreatic graft according to Hédon.[1] From Jan. 29, 1913, on, took daily records of the empty stomach 24 hours after the last meal. The types of contraction on the succeeding days were as follows:

Jan. 31, 1913: Types I and II (Fig. 4).

Feb. 1, 1913: Types I and II.

Feb. 2, 1913: Type III.

Feb. 3–Feb. 7 (inclusive): Type III.

Feb. 8, 1913: Removal of the subcutaneous pancreatic graft under light ether anesthesia. Wet weight of graft: 3 gm. Intense

Dog II. Figure 4. Jan. 31, 1913. Four-fifths the original size. Type II contractions indicating moderate hunger. The horizontal line represents 0 mm. bromoform pressure.

polyuria and glycosuria followed this operation immediately. (See Table II.)

Feb. 9–12 (inclusive): The contractions during this period conformed to the type described as type III. In spite of the fact that the stomach was in a high state of tonus, small tetany periods of several minutes' duration were noticed in addition.

Feb. 13–15 (inclusive): The contractions were the most pronounced (type III) seen in any dog under any condition up to that time. Figure 5 represents a portion of the tracing taken on Feb-

[1] Hédon: Archives internationales de physiologie, 1911, x, p. 350.

TABLE II

Dog II							
Date 1913	Body weight kg.	Food in gm.	Food in gm. per kg. body weight	Urine cc.	Sugar	Type of contractions	Remarks
Jan. 22							Pancreatectomy with graft
Jan. 27	5.440			270			
Jan. 28	5.100	264	51.7	180	1.92%		
Jan. 29	5.000			80			Gastrostomy
Jan. 30	4.835	165	34.3				
Jan. 31	4.900	161	32.8	150		I and II	
Feb. 1	4.700	165	35.1	60		I and II	
Feb. 2	4.500	158	35.1	40		III	
Feb. 3	4.500	187	41.5	75		III	
Feb. 4	4.280	395	91.8	35		III	

Feb. 5	4.300	259	60.2	40		III	
Feb. 6	4.200	207	49.2	40		III	
Feb. 7	4.100	280	68.2	55		III	
Feb. 8	4.100	206	50.	60		No record	Removal of graft
Feb. 9	4.100	150	36.5	175	5.31%	III	
Feb. 10	3.900	106	27.1	160	7.14%	III	
Feb. 11	3.700	137	37.0	83	5.55%	III	
Feb. 12	3.550	279	78.5	130	3.12%	III	
Feb. 13	3.500	201	57.4	70	6.25%	III	
Feb. 14	3.400	202	59.4	125	4.1%	III	
Feb. 15	3.240	105	32.4	90	2.5%	III	
Feb. 16	2.980	Refused food					
Feb. 17	2.980			15 cc. in bladder	Trace		Dead

ruary 13. The empty stomach is in incessant motion. In addition, there are seen short tetany periods. The strip of the tracing which is reproduced as Figure 5 represents the culmination of a tetany period lasting about 25 minutes. It will be noticed that at *X* the dog whined as if in pain. The tracings taken on the 14th and 15th of February are similar. On the 15th the dog could scarcely walk; was cold to the touch. Rectal temperature 97.6° F. As seen from Figure 6, hunger contractions were marked (type III).

Dog II. Figure 5. Feb. 13, 1913. Two-thirds the original size. The culmination of a tetany period in the diabetic animal lasting about 20 minutes. Smaller tetany periods are likewise shown. Thoughout a type III rhythm on a high tonus. At *X* dog whined as if in pain. Horizontal line represents 0 mm. bromoform pressure.

At the conclusion of the experiment the dog, with considerable difficulty, ate 105 gm. of meat.

Feb. 16–17: Dog could scarcely raise head. Rectal temperature 90.3° F. Obtained no contractions of the empty stomach. Dog refused food and drink. Was found dead on the morning of the 17th. Table II gives in detail the results of this experiment.

Discussion

The results obtained from the two dogs were so clear cut that further experimentation was considered unnecessary. Both dogs during pancreatic diabetes ate well — more than a normal dog of the same weight would eat. They continued to eat when too weak

to stand unsupported and when they were cold to the touch (rectal temperature 90.3–92.5° F.). There can be no question that they ate because they were *hungry;* for the voracity exhibited was the result of powerful contractions of the empty stomach. The contractions were at least as powerful and possibly more powerful than the contractions seen subsequently in normal dogs starved for 10 to 12 days. One cannot escape the opinion that dogs dying

Dog II. Figure. 6. Feb. 15, 1913. Two-thirds the original size. Tracing obtained from the empty stomach less than two days before death. Throughout type III contractions on a high tonus. Dog could scarcely walk. Ate 105 gm. meat — the last meal before death, which followed two days later. The bottom of the cut may be taken as the line representing 0 mm. bromoform pressure.

from pancreatic diabetes are animals in the most extreme state of inanition.

After the appearance of pancreatic diabetes, Dog I consumed on an average 67.5 gm. meat per kilo body weight, the extreme being 48.9 and 95.8 gm. (Table I). Dog II did not exhibit as great a voracity. Prior to the removal of the graft this dog ate daily on an average 48.8 gm. per kilo body weight. After glycosuria had been induced he consumed on an average 51.1 gm. per kilo body weight (Table II). This slight increase (1.3 gm.) is insignificant. From an examination of Table II it is apparent that Dog II, before the removal of the graft, was not a normal animal. It is true that removal of the graft (3 gm.) was followed by an intense glycosuria and polyuria which persisted till two days before death. In addition, the dog lost its playful disposition and entered into that

apathetic state so characteristic of dogs dying from the effects of pancreatic diabetes. On the other hand, the "normal" dog *was losing weight rapidly*, in spite of the fact that the dog *ate more meat* in gm. per kilo body weight than a normal dog. Three normal dogs whose average weight was 7.65 kg. (extremes: 6.2–8.52 kg.) ate daily during a period of 37 days on an average of 22.48 gm. of meat per kilo body weight (extremes: 16.51–28.05 gm.). Before removal of the pancreatic graft, Dog II ate daily 48.9 gm. meat per kilo body weight, more than twice the amount consumed by a normal animal. Owing to the presence of the small pancreatic graft only a transient glycosuria followed extirpation of the greater portion of the pancreas. However, two of the striking symptoms of pancreatic diabetes had already appeared; namely, rapid loss in weight and polyphagia. The polyphagia of pancreatic diabetes was, therefore, well developed before a permanent glycosuria was established. The latter hastened the exitus without affecting the polyphagia. This polyphagia resulted from the most intense *hunger* contractions ever observed in animals up to that time.

The great activity of the stomach in these otherwise decrepid animals was a striking phenomenon. It was the *smooth* musculature of the stomach which showed untiring activity at a time when the skeletal musculature of the body was exceedingly susceptible to rapid fatigue. In fact, the strength of the stomach contractions increased as the power of the voluntary musculature diminished; for the stomach was in incessant motion at a time when the dog was too weak to stand unsupported and could not chew its food without taking an occasional rest.

Résumé

A dog dying from pancreatic diabetes consumes more food per kilo body weight per day than does a normal animal. This polyphagia of pancreatic diabetes has been mentioned by most observers. It was not clear, however, whether the polyphagia resulted from a true sense of hunger or was a morbid desire or perverted appetite brought on by this diseased condition. But from the evidence presented in this paper it is certain that this polyphagia is the result of true hunger; for (*a*) the hunger contractions not

only persist after removal of the pancreas, but (*b*) become more intense with the progress of the disease, just as the voracity of the animal increases during the terminal stages of the disease. The animal dies in an extreme degree of inanition and eats ravenously because of the increased intensity of the gastric hunger contractions.

THE INFLUENCE OF THE RATE OF URINE FLOW ON THE SECRETION OF URIC ACID

By J. H. ROBERTSON

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THE paper published by Sharpe [1] last year from this laboratory indicated that even with the methods of urinary analysis which he employed, some light on the factors influencing the secretion of uric acid might be gained if hens, which have a urine twice or more as rich in that constituent as dogs or man, were used. At the suggestion of Professor Henderson this investigation was immediately undertaken.

Since this work was begun, the publication of Folin's new methods have made the problem even more approachable. The uric acid estimations in some of the preliminary experiments were made by Kowarski's modifications of the Hopkins' method, which was found to give accurate estimations, if the piperidin solution were standardized each time that it was employed, and if the titrations were made rapidly. An attempt was made to improve the method by using piperidin, a much less volatile base, but unfortunately no indicator could be found that gave a sufficiently sharp end-point to both this base and uric acid.

On the publication of the colorimetric method of Folin and Macallum,[2] it was tested and found to give satisfactory results; and as soon as the improved method of Folin and Denis [3] was published, it was also proved, and appearing satisfactory, was adopted. Difficulties were encountered with one or two cases of urine from dogs. In these the addition of the silver lactate reagent caused a dense precipitate, which turned black in from twenty to sixty seconds, and the amount of uric acid found was much less

[1] SHARPE: this Journal, 1912, xxxi, p. 75.

[2] FOLIN and MACALLUM: Journal of biological chemistry, 1912, xiii, p. 363.

[3] FOLIN and DENIS: Journal of biological chemistry, 1913, xiv, p. 95.

than that expected. Other samples to which larger amounts of the silver reagent were added gave equally bad results, and on estimating the amount of uric acid with the Folin-Macallum method, nearly six times as much uric acid was found as with the Folin-Denis method. The small amount of urine remaining in the first case was taken to Dr. Raper, to whom the author wishes to express his thanks for the assistance given on this and other occasions, and he suggested that the reaction might be due to thiosulphates. Various tests were made that indicated their presence, but the quantity of urine was too small to make a quantitative study. Dogs' urine, to which thiosulphates were added, gave a somewhat similar reaction. The amount of other salts present seemed also to influence the reaction.

An estimate of the amount of uric acid in the blood of hens was made in two cases. In Experiment 14, 6.16 mgm. were found in 100 gm. of blood, and in the other 5.15. The average reported by Folin and Denis[1] was 4.9. The higher result in these cases may be due to the fact that the animals had previously secreted a considerable amount of urine. In the blood of a dog, 0.67 mgm. was found in 100 gm., and in that of a cat 0.205, which agrees very closely with the amount found by Folin.

In the experiment illustrated by Figure 3 in Sharpe's paper, it seemed that injections of uric acid dissolved in piperazin caused a considerably greater secretion of urine than would have been expected from the same amount of piperazin alone, and this suggested that the excretion of uric acid was accompanied by a considerable loss of water. This is hardly what might be expected from a consideration of the histological picture presented by the work of those who have investigated the subject microscopically.[2] A brief review of these papers will make this clear.

Sauer injected into rabbits, which normally secrete very small amounts of uric acid, a solution of uric acid in piperazin. The in-

[1] FOLIN and DENIS: Journal of biological chemistry, 1913, xiv, p. 29.

[2] See ERBSTEIN and NICOLAIER: Archiv für pathologische Anatomie, 1896, cxlvi, p. 377; SAUER: Archiv für mikroskopische Anatomie, 1899, liii, p. 218; ANTEN: Archives internationales de pharmacodynamie et therapie, 1901, viii, p. 455; COURMONT and ANDRÉ: Journal de physiologie et pathologie générale, 1905, vii, p. 197; TODARO: Archives italiennes de biologie, 1902, xxxviii, p. 33.

jections are followed by a marked flow of urine and by the secretion of uric acid. The piperazin alone would cause a marked urine flow. The kidneys were examined fresh, and uric acid particles were described as appearing in the cells and lumina of the convoluted tubules, but none in the glomeruli or its capsule. The cells of the loop of Henle and of the collecting tubules were free from particles, but these were to be seen in their lumen. The fine particles were found only in the outer half of the cells, and the striated border appeared as if broken by their extrusion. To prove that the particles in the lumina of the lower tubules were due to washing down from above, some experiments were performed in which a part of the cortex was destroyed, and then the injection given; in the lower tubules of the destroyed area no particles were found, though the convoluted tubules were full of them.

Anten injected the kidneys of dogs from the renal artery with an ammoniacal silver chloride solution, the excess of which was washed out with saline, and the kidneys were then fixed in alcohol. He found the cells of the convoluted tubules and the wide ascending limb of Henle's loop filled with fine particles, but these occurred rarely in the glomerulus, and never in the space of Bowman's capsules, nor in the other capsules.

Courmont and André extended the observations of Anten to representatives of various vertebrate types. They fixed first, in an absolute alcohol, glacial acetic acid and chloroform mixture, and cut sections which they treated with hydrochinon and with silver nitrate. They made controls with ammoniacal silver solution. They found uric acid granules in the position described by the previous authors, save that they found them also in the cells of the descending limb of Henle in the dog. The position of the granules in the outer halves of the cells corresponded to the position of the so-called crystalloid vacuoles described by Gurwitsch. They thought that they were able to show some effect on the particles when they injected pilocarpine previously to removing the kidney.

Todaro describes uric acid particles collected in the cells of the kidney canals of tunicates and says that these are gradually carried to the surface and there excreted in a slimy mass.

Tribondeau [1] similarly describes how the contents of the vacu-

[1] TRIBONDEAU: Comptes rendus de la Société biologique, 1901, liii, p. 1188.

oles in the kidney cells of snakes pass in the forms of drops through the striated border of the cells and appear in the lumen in clumps.

The experiments were first carried out on hens alone. The technique was the same as that described by Sharpe.[1] As was noted by him, marked variations in the rate of urine flow often occurred without assignable cause, though this may in part be explained as due to the changes in blood pressure, as a constant record of this factor was rendered difficult by the occurrence of marked rings of constriction in the exposed carotid arteries which at times made the manometer record of little value.

Protocols or curves illustrating them are given only of typical experiments, though many more, some 25 in all, were performed.

EXPERIMENT 3

HEN, WEIGHT 2 K., URETHANE AND ETHER

Time in min.	Cc. urine per min.	Mgm. uric acid per min.	Mgm. uric acid per cc.	Urine in cc.
32	2.50	4.15	1.66	7.5
36	2.35	3.61	1.54	9.5
42	1.61	2.19	1.36	9.7
50	1.31	1.87	1.43	10.5
62	0.76	0.988	1.30	3.8
68	3 cc. of a 5% solution of piperazin			
76	0.80	1.16	1.45	4.0
83	0.58	0.84	1.45	2.9
86	0.60	0.85	1.43	3.0
91	0.44	0.62	1.41	2.2
96	0.32	0.45	1.43	1.6
101	0.32	0.44	1.38	1.6
125	50 mgm. uric acid dissolved in 3 cc. 5% piperazin			
136	0.17	0.66	1.54	5.9
146	0.14	0.27	1.96	1.4
161	2 cc. 10% piperazin			

[1] SHARPE: *Loc. cit.*

174	0.12	0.26	2.17	2.9
204	2 cc. 10% piperazin			
224	0.078	0.15	1.96	3.9
224	3 cc. 20% Na_2So_4			
234	0.22	0.435	1.98	2.2
234	40 cc. Ringer's solution			
245	80 cc. Ringer's solution			
262	0.36	0.59	1.66	10.0
272	0.58	0.14	0.25	5.8

EXPERIMENT 6

ROOSTER, WEIGHT 3 K., URETHANE AND ETHER

Time in min.	Cc. urine per min.	Mgm. uric acid per min.	Mgm. uric acid per cc.	Cc. urine
9	0.84	1.20	1.43	7.6
15	1.10	2.09	1.90	6.6
25	20 mgm. caffeine sodium benzoate			
26	0.54	1.13	2.10	6.0
30	1.35	1.93	1.43	5.4
34	1.35	1.22	0.91	5.4
38	1.37	1.37	1.00	6.5
39	20 cc. Ringer's solution			
42	2.50	1.66	0.66	10.0
46	3.50	2.06	0.59	14.0
50	3.00	1.92	0.64	12.0
54	2.00	2.00	1.00	8.0
58	1.45	1.98	1.37	5.8
62	1.12	1.99	1.78	4.5
62	2 cc. 20% Na_2SO_4 solution			
70	0.88	1.81	2.06	7.0
78	0.64	1.38	2.17	5.1

78	2 cc. 20% Na_2SO_4 solution			
89	0.48	1.04	2.17	5.3
93	1.95	1.56	0.80	7.8
97	1.90	0.95	0.50	7.5
104	1.57	0.97	0.62	11.0
112	1.00	1.33	1.33	8.0
120	0.60	0.90	1.51	4.8
128	0.36	0.75	2.10	2.9
138	20 cc. Ringer's solution			
140	0.32	0.64	2.00	3.8
148	0.74	1.48	2.00	5.9
148	20 cc. Ringer's solution			
156	0.94	1.44	1.54	7.5
168	0.87	1.44	1.66	10.5
180	0.65	1.07	1.66	7.8
201	0.39	0.82	2.10	8.2
232	0.30	0.60	2.00	9.5
272	0.27	0.51	1.90	11.0
312	0.18	0.34	1.90	7.2
366	0.10	0.26	2.66	5.8

If in the protocols the flow of urine per minute be compared with the output of uric acid, a very striking general parallelism may be noted. Increased output of fluid is accompanied by increase in uric acid. This was quite striking in No. 14, which is shown in the form of a curve (Fig. 1). In other cases, while the parallelism is true in a broad sense, it is not true in detail; for example, in Experiment 6, between the 50th and 65th minutes the uric acid per minute remains high, while the flow is falling off very rapidly.

On comparing the curves of urine flow per minute and that of uric acid per cubic centimetre of urine, the latter is in general the obverse of the former; but this contrast is by no means so exact as

is the parallelism between urine flow and uric acid output per minute. For example, in Experiment 3 there is at first a fall in the uric acid accompanying the fall in urine flow. This fall of uric acid comes to an end about the 62d minute, while the fall in water output continues. Indeed, the succeeding portion of the curve would suggest that the injection of piperazin had led to a special excretion

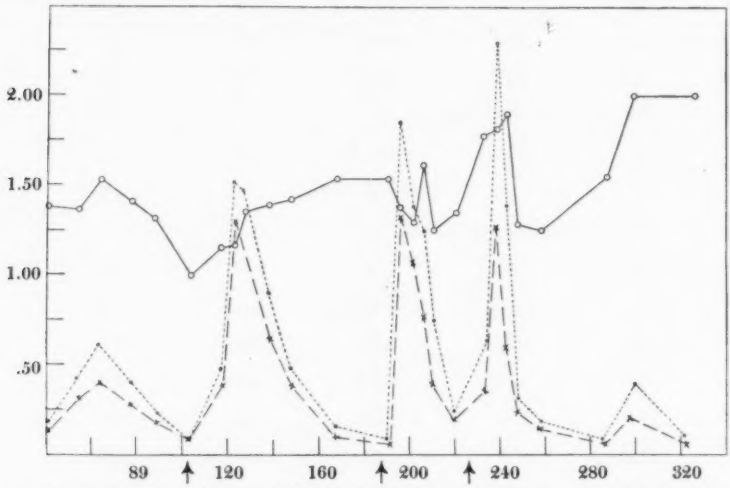

FIGURE 1. — Experiment 14. Increased output of urine is accompanied by increase in uric acid. The full line shows milligrams of uric acid per cubic centimetre of urine. The dotted line shows milligrams of uric acid per minute. The dashes show cubic centimetres of urine per minute. The abscissae mark time in 20 minute intervals. The ordinates mark milligrams of uric acid per minute and cubic centimetres of urine per minute respectively. The arrows mark adrenalin and the asterisk marks caffeine.

of uric acid unaccompanied by much water. In other experiments with this drug such results were not so strikingly obtained, and no conclusion has been reached on this point as yet. Sharpe had noticed that when the blood pressure was low and urine secretion tardy, an injection of adrenalin often produced a considerable diuresis; and in consequence, in Experiment 14 (Fig. 1), three injections of adrenalin were given. It will be noted that the increase in flow of urine is surpassed by the output of uric acid per minute, and that the curve of uric acid per cubic centimetre does not fall distinctly with the increase of urine flow, and indeed, after the third injection, rises in a definitely independent fashion, which

again suggests a possibly specific excretory effect. This result might, perhaps, be more simply explained by the marked changes in blood distribution produced by the cardiac and vascular effects of the drug.

In the experiments reported upon in this paper, changes in the rate of urine flow succeeded the injection of normal saline (Ringer's solution), caffeine, hypertonic sodium sulphate, piperazin, adrenalin, 2-phenyl-chinolin-4-carbonic acid (atrophan), potassium nitrate (2% solution), and barium chloride, and characteristically with all these, the rate of uric acid production varied with the urine flow. It will be readily granted that all these drugs can hardly produce the effects observed directly, but probably acted indirectly by influencing the blood flow through the gland.

Although the blood flow through the kidney in general runs parallel with the urine production, this is not true under all conditions; as, for example, in experiments reported by Barcroft and Brodie[1] and by Loewi.[2] Also the output of uric acid might well be influenced by the blood flow through the organ in a manner quite different from the urine production, and in consequence some experiments were undertaken in which this factor was also recorded.

For this purpose the anatomical relations of the kidney in hens made their employment impossible, and large dogs were used. It was imperative that any method employed to measure the blood flow should be one that produced as little disturbance of metabolism and circulation as possible. The most exact method of measurement is that described by Barcroft and Brodie,[3] in which the venous flow is measured by allowing it to run along a graduated glass tube inserted into the vena cava below the kidney. This method, however, owing to the obstruction of the cava alone, quite apart from the complete evisceration which these workers employed, made the method unavailable for our purpose. Plethysmography alone, as shown by Loewi,[4] cannot be entirely relied

[1] Barcroft and Brodie: Journal of physiology, 1905, xxxiii, p. 67.

[2] Loewi: Archiv für experimentelle pathologie und pharmacologie, 1905, liii, p. 16.

[3] Barcroft and Brodie: Journal of physiology, 1904, xxxii, p. 18.

[4] Loewi: *Loc. cit.*

upon. The method employed was that described by Brodie and Russell,[1] in which the plethysmograph containing the kidney is connected with a delicate recorder writing upon a rapidly revolving drum, and the rate of flow measured by the rate of dilatation of the organ, when the kidney vein is temporarily constricted. Results of a typical experiment of this type are shown in the protocol for Experiment 21.

EXPERIMENT 21

DOG, MALE, WEIGHT 20 K., MORPHINE, ETHER

Time in min.	Cc. urine per min.	Mgm. uric acid per min.	Mgm. uric acid per cc.	Amount urine cc.	Time to dilate kidney
12					1.40
26					1.65
33	0.1	0.1	1.0	3.3	
40					1.75
58	0.09	0.09	1.0	2.3	
59	Pituitary extr. 1 cc.				
60					1.45
68					1.00
84	0.09	0.086	0.96	2.3	
88					1.55
94	0.23	0.24	1.05	2.3	
96					1.70
98	Saline				
101	0.36	0.30	0.85	2.5	
105	0.80	0.37	0.47	3.2	1.10
109	$BaCl_2$				1.18
110	0.44	0.18	0.41	2.2	
112					1.98
132					1.60
134	0.09	0.06	0.67	2.2	1.62

[1] BRODIE and RUSSELL: Journal of physiology, 1905, xxxii, proc. xlvii.

150					1.85
152	0.16	0.15	0.96	3.0	
160					1.80
161	Caffeine 2% solution				
162					1.55
166	0.21	0.225	0.75	3.0	
170					1.25
180					1.95
182	0.26	0.25	0.96	4.2	
196	$BaCl_2$				1.98
197	0.19	0.18	0.96	2.8	
201					2.40
206					1.90
213	0.14	0.14	1.0	2.3	1.75
214	N_2SO_4				
220	0.77	0.53	0.7	5.4	1.20
224	1.35	0.27	0.20	5.4	
230					1.90
231	0.94	0.20	0.23	6.6	
238					2.00

In this experiment the time is calculated during which the kidney would be dilated by an arbitrary amount, which was approximately 2.5 cc., as only comparative figures were required. In this, as in the other experiments of this type, a general parallelism between the rate of flow of urine and uric acid is evident, and in general the rate of blood flow increased with increasing urine production. In none of the experiments, however, were we successful in producing a change in uric acid secretion which was sufficiently independent of urine flow to suggest any specific effect of the drugs injected; nor could any dependence of the rate of uric acid secretion on blood flow alone be established, as in all cases the variation in urine production paralleled the changes in blood flow.

Summary

In spite of the accuracy of the methods introduced by Folin for the determination of uric acid, the experiments reported above show clearly the difficulty in determining whether the excretion of uric acid by the kidney is a specific process of secretion accompanied by a considerable quantity or by very little water. Nor have these experiments been successful in definitely establishing whether increased water excretion or the change in the blood flow through the gland is primarily responsible for the parallelism between the increase in urine flow and uric acid excretion. Certain of the experiments indicate that the uric acid excretion may vary independently of the urine flow, and that increased uric acid excretion does not necessarily lead to much increase in the amount of urine. It is hoped that further experimentation will give a more definite result.

STUDIES IN FATIGUE

III. The Fatigue Threshold as Affected by Adrenalin and by Increased Arterial Pressure

By CHARLES M. GRUBER

[From the Laboratory of Physiology in the Harvard Medical School]

IN a previous paper I showed that fatigue increases the normal threshold stimulus, on an average, between 100 and 200 per cent, and may increase it more than 600 per cent, whether taken from the normal muscle directly or from the nerve-muscle; that a subsequent rest varying from 15 minutes to two hours restores the muscle and nerve-muscle to their original threshold irritability, and that the time required for restoration depends upon the duration of the fatigue and the condition of the animal.[1]

That the removal of the suprarenal capsules has a marked effect upon the efficiency of striated muscle has long been known. The first conclusive evidence showing that adrenal extract has a bettering effect on the muscular contraction was given by Oliver and Schäfer.[2] After injecting the extract subcutaneously into a frog and then excising the gastrocnemius muscle, these authors observed a curve of contraction which was higher and longer than that of the corresponding muscle not exposed to the extract. A similar prolongation of the muscle curve was observed after the extract was injected intravenously into a dog. Dessy and Grandis claimed that adrenal extract produces a beneficial effect on fatigued muscle either when injected subcutaneously into a salamander or when added to the solution in which the isolated muscle is contracting.[3] Radwánska found in frogs that the beneficial action of adrenalin is far greater when the muscle is stimulated through its

[1] Gruber: this Journal, 1913, xxxii, p. 438.

[2] Oliver and Schäfer: Journal of physiology, 1895, xviii, p. 263.

[3] Dessy and Grandis: Archives italiennes de biologie, 1904, xli, p. 231.

nerve than when stimulated directly.[1] Further evidence tending toward the same conclusion was offered by Panella, who observed this phenomenon of reinforced activity in striated muscle in heterothermic animals, and also in homothermic animals the conditions of which were rendered by experimental procedures like those of the heterothermic.[2] Cannon and Nice more recently demonstrated that adrenalin injected in small doses or secreted during splanchnic stimulation causes an improvement in the activity of fatigued muscle.[3] In my first paper of this series I confirmed their results and showed, in addition, the quantitative relation between arterial pressure and the height of the fatigue curve. In conclusion I referred to this statement made by Cannon and Nice: "The observations here recorded, however, indicate that adrenalin may operate favorably in making more effective the nervous impulses delivered to fatigued muscles." [4]

The question whether or not this increase in muscular efficiency after an injection of a small dose of adrenalin, or after splanchnic stimulation with or without the adrenal glands intact, is the result of lowering the threshold irritability has been the subject of this investigation.

The Method

In some cases the animals (cats) were anesthetized with urethane (2 gm. per kilo body weight by stomach), in others they were decerebrated. The nerve-muscle preparation was the tibialis anticus muscle and the nerve supplying it the peroneus communis. The stimulating current for fatigue was a maximal break induction shock obtained from a vulcanite disc interrupter. The rate of stimulation was 120 or 240 per minute. The rate was kept uniform throughout each experiment. Threshold stimuli were determined by the Martin method, in which the threshold is calculated in β units.[5]

[1] Radwánska: Anzeiger der Akademie, Krakau, 1910, pp. 728–736. Reviewed in Centralblatt für Biochemie und Biophysik, 1911, xi, p. 467.

[2] Panella: Archives italiennes de biologie, 1907, xlviii, p. 462.

[3] Cannon and Nice: this Journal, 1913, xxxii, p. 49.

[4] Gruber: this Journal, 1913, xxxii, p. 221; Cannon and Nice: *Loc. cit.*, p. 59.

[5] Martin: Measurement of Induction Shocks, New York, 1912, pp. 71–93. For detailed description of the method employed in this work see Gruber: this Journal, 1913, xxxii, p. 438.

A mercury manometer was employed to record the arterial pressure, which was taken, in every case, from a cannula in the right carotid artery. When adrenalin was injected or the splanchnic nerves stimulated, the blood pressure was allowed to return to normal before the threshold stimulus was determined.

The method for stimulating the left splanchnic nerves was that of Cannon and Nice.[1]

Through a cannula placed in the left external jugular vein the adrenalin was injected *slowly*, usually in doses of 0.1 cc. of a 1:100,000 solution, and never in doses exceeding 0.5 cc. Through another cannula placed in the right external jugular vein amylnitrite was, in some experiments, injected in doses sufficiently large to cause a marked fall in blood pressure.

Experiments were also performed in which the hind leg was irrigated, at a constant pressure of 95 mm. of mercury, through cannulas in the external iliac artery and vein. The medium for irrigation was a warm (38.5–40° C.) Ringer's solution. The adrenalin was injected into the running solution close to the arterial cannula.

In an attempt to determine whether the action of adrenalin is on the muscle or on the nerve-endings or both, a number of experiments were performed on animals in which a section (2 cm. long) of the left peroneus communis nerve was removed aseptically 6 to 21 days previous to the experiment.

The Effect of Adrenalin upon the Fatigue Threshold

The normal threshold stimulus of the peroneus communis nerve varied in the animals used from 0.35 to 5.45 β units, with an average in nine experiments of 1.3. (See Table I.) This average is the same as that found by E. L. Porter for the radial nerve of the spinal cat, and as that cited in an earlier paper of this series for the peroneus communis of the decerebrate cat.[2] For the tibialis anticus muscle, in which the nerve-endings were intact, the threshold varied from 6.75 to 49.3 β units, with an average in the nine

[1] Cannon and Nice: *Loc. cit.*, p. 47.

[2] E. L. Porter: this Journal, 1912, xxi, p. 149; Gruber: this Journal, 1913, xxxii, p. 443.

TABLE I

THE EFFECT OF ADRENALIN UPON THE FATIGUE THRESHOLD STIMULUS OF THE TIBIALIS ANTICUS IN DECEREBRATE CATS. MEASUREMENTS TAKEN BY THE MARTIN METHOD FROM (I) THE PERONEUS COMMUNIS NERVE AND (II) THE MUSCLE DIRECTLY

I									II				
Length of Fatigue	Rate of Stimulation	Initial Tension of Spring	Normal β	Fatigue β	Fatigue β after Adrenalin	Increase in per cent	Recovery of the Threshold in per cent	Number of cc. of Adrenalin injected	Normal β	Fatigue β	Fatigue β after Adrenalin	Increase in per cent	Recovery of the Threshold in per cent
2 hr. 25 min.	120	200	1.25	4.23	0.84	238	112	0.1	20.67	74.5	58.5	261	36
1 hr.	120	120	0.62	0.89	0.79	43	37	0.1	30.0	51.6	38.0	72	62
46 min.....	120	200	0.45	0.82	0.74	82	21	0.5	24.9	84.4	70.2	239	24
1 hr.	120	120	0.67	1.0	0.87	49	39	0.1	10.0	30.6	18.0	206	61
1 hr.	240	120	1.79	2.27	2.07	27	42	0.3	14.7	47.0	21.7	220	78
10 min.....	120	120	0.62	0.79	0.59	27	118	0.6	30.0	130.0	101.0	334	29
1 hr.	120	120	0.68	0.88	0.54	29	170	0.2	6.75	20.3	6.5	201	101
15 min.....	120	120	0.35	0.65	0.4	86	83	0.1	13.0	21.1	17.8	62	40
[1]4 hr.	120	200	[1]5.45	17.9	9.55	229	67	0.1	49.3	76.7	50.2	56	91
Average			1.3	3.3	1.8	154	75		22.2	59.6	42.4	169	46

[1] Urethane anesthesia.

experiments of 22.2. This is slightly higher than that cited for this same muscle in the paper mentioned above. By fatigue the threshold of the nerve-muscle was increased from an average of 1.3 to an average of 3.3 β units, an increase of 154 per cent. The muscle increased from an average of 22.2 to an average of 59.6, an increase of 169 per cent. (See Table I.) After an injection of 0.1 to 0.5 cc. of adrenalin (1:100,000) the fatigue threshold was decreased within five minutes in the nerve-muscle from an average β of 3.3 to 1.8, a recovery of 75 per cent, and in the muscle from an average β of 59.6 to 42.4, a recovery of 46 per cent. (See Table I.)[1] To prove that this effect of adrenalin is a *counteraction of fatigue*, I determined the threshold stimulus for muscle and nerve-muscle in non-fatigued animals before and after adrenalin injection. I found that in these cases no lowering of threshold occurred, a result in marked contrast with the pronounced and prompt lowering induced in fatigued muscles by this agent.

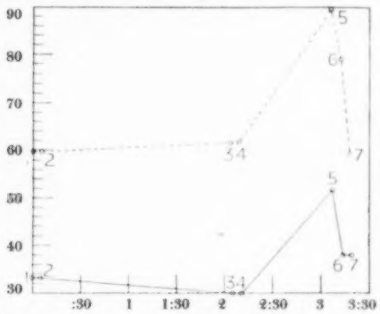

FIGURE 1.—A curve plotted from the data of one experiment. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the muscle, the broken line that of the nerve-muscle. The nerve-muscle curve is magnified 100 times; that of the muscle is normal.

(1) Normal threshold stimulus. (2) Threshold five minutes after an intravenous injection of 0.1 cc. of adrenalin (1:100,000) without previous fatigue. (3) Threshold after a rest of two hours. (4) Threshold five minutes after an injection of 0.2 cc. of adrenalin (1:100,000) without previous fatigue. (5) Threshold after one hour's fatigue. The muscle contracted 120 times per minute against a spring having an initial tension of 120 gm. (6) Threshold five minutes after an injection (0.1 cc.) of adrenalin (1:100,000). (7) Threshold five minutes after another injection of adrenalin (0.5 cc. of a 1:100,000 solution).

Figs. 1 and 2, plotted from the data of two of the experiments, show the relative heights of the threshold before and after an injection of adrenalin. The two readings of the threshold, one from the nerve supplying the muscle,

[1] The fatigue thresholds here cited do not always indicate the highest level reached. In some cases the reading was made after a period of rest. But this gives an indication of the action of adrenalin.

the other from the muscle directly, served to show that there was no fault in the electrodes. The continuous line in the curve represents the threshold (in β units) of the muscle, the broken line that of the nerve-muscle. The threshold of the nerve-muscle is magnified 100 times in Fig. 1 and 10 times in Fig. 2. In Fig. 1 (at 2 and 4) the threshold was taken after an intravenous injection of 0.1 and 0.2 cc. of adrenalin respectively.

These examples show that adrenalin does not affect the threshold of the normal non-fatigued muscle when taken either from the

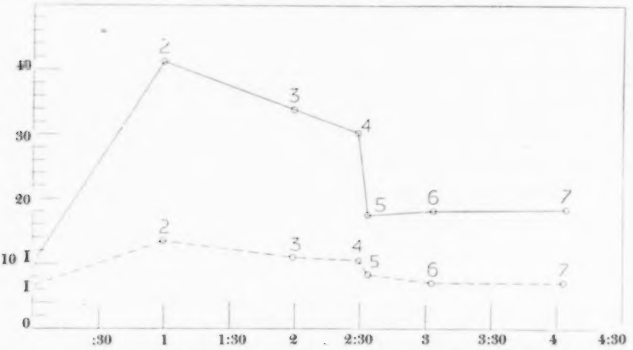

FIGURE 2.—A curve plotted from the data of one experiment. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the muscle, the broken line that of the nerve-muscle. The curve of the nerve-muscle is magnified ten times; that of the muscle is normal.

(1) Normal threshold stimulus. (2) The threshold after one hour's fatigue. The muscle contracted 120 times per minute against a spring having an initial tension of 120 gm. (3 and 4) Thresholds after rest; after 60 minutes (3), and after 90 minutes (4). (5) Threshold five minutes after an injection of adrenalin (0.1 cc. of a 1:100,000 solution). (6 and 7) Thresholds after rest; after 60 minutes (6), and after 90 minutes (7).

muscle directly or from the nerve-muscle. In Fig. 1 (at 3) the threshold was taken after two hours' rest. This confirms E. L. Porter's observation that the threshold may remain constant for a very long time when left in a state of rest.

In Fig. 1 the normal threshold stimulus was increased by fatigue (at 5) — the muscle pulling 120 times a minute for one hour on a spring having an initial tension of 120 gm. — from 30.0 to 51.6 β units, an increase of 72 per cent; and in the nerve-muscle from 0.62 to 0.89 β units, an increase of 46 per cent. In

Fig. 1 the threshold (at 6) was taken five minutes after injecting 0.1 cc. of adrenalin (1:100,000). The threshold of the muscle was lowered from 51.6 to 38.0 β units, a recovery of 62 per cent; that of the nerve-muscle from 0.89 to 0.79 β units, a recovery of 37 per cent. After another injection of 0.5 cc. of adrenalin the thresholds (at 7) were taken; that of the nerve-muscle dropped to normal — 0.59 β units — a recovery of 100 per cent, and that of the muscle remained unaltered — 26 per cent above its normal threshold.[1]

In Fig. 2 the threshold (at 5) was taken five minutes after an injection of 0.1 cc. of adrenalin. The drop here was as large as that shown in Fig. 1. The threshold taken from the muscle directly was lowered from 30.6 to 18 β units, a recovery of 61 per cent; the nerve-muscle from 1.08 to 0.87 β units, a recovery of 51 per cent. That this sudden decrease cannot be due to rest is shown in the same figure (at 3 and 4). These readings were made after 60 and 90 minutes' rest respectively. The sharp decline in the curve (at 5) indicates quite distinctly the influence of adrenalin upon fatigue threshold irritability.

Splanchnic Stimulation

The average normal threshold taken from the peroneus communis nerve in a series of eleven experiments was 3.4 β units, and directly from the tibialis anticus muscle, in which the nerve-endings were intact, it was 29 β units. The former average threshold was increased by fatigue to 5.96, an increase of 75 per cent, and the latter to 58.3, an increase of 101 per cent. Stimulation of the left splanchnic nerves, in some cases for 30 seconds, in others for one minute, reduced this average fatigue threshold in the nerve-muscle from 5.96 to 4.9, a recovery of 41 per cent, and in the muscle from 85.3 to 40.4 β units, a recovery of 62 per cent. (See Table II, *A*.)

Fig. 3 is a curve plotted from the data of one of the experiments, showing the effect of splanchnic stimulation upon the threshold stimulus. The broken line is the curve of the nerve-muscle,

[1] This discrepancy may be due to variation in placing the electrodes in the muscle. The results from readings on the nerve are more likely to be uniform and reliable.

TABLE II

THE EFFECT OF LEFT SPLANCHNIC STIMULATION UPON THE FATIGUE THRESHOLD STIMULUS OF THE TIBIALIS ANTICUS MUSCLE IN CATS IN URETHANE ANESTHESIA. MEASUREMENTS TAKEN BY THE MARTIN METHOD FROM (I) THE PERONEUS COMMUNIS NERVE AND (II) THE MUSCLE DIRECTLY. (*A*) THE ADRENAL GLANDS ARE INTACT AND (*B*) THE LEFT OR BOTH ADRENAL GLANDS ARE TIED OFF.

	I									II				
	Length of Fatigue	Rate of Stimulation	Initial Tension of Spring	Normal β	Fatigue β	Fatigue β after Splanchnic Stimulation	Increase in per cent	Recovery of the Threshold in per cent	Length of Splanchnic Stimulation in seconds	Normal β	Fatigue β	Fatigue β after Splanchnic Stimulation	Increase in per cent	Recovery of the Threshold in per cent
A	15 min.	120	120	1.79	2.9	2.36	62	48	30	22.3	51.8	24.2	115	94
	1 hr.	120	120	2.36	2.88	2.1	22	120	30	19.3	30.4	27.2	57	31
	15 min.....	120	120	2.1	2.4	2.1	14	100	60	30.2	39.1	37.0	31	23
	1 hr.	120	120	1.1	1.65	1.12	50	91	30	32.1	70.2	43.7	119	69
	15 min.....	120	120	1.79	2.1	1.76	17	109	60	12.5	21.8	16.3	74	59
	45 min.	240	120	1.45	2.05	1.46	41	98	30	12.53	39.0	27.0	211	45
	5 min.....	240	120	1.35	1.6	1.41	19	54	60	16.4	30.6	18.6	86	83
	[1]1 hr.....	240	150	2.5	6.8	3.8	170	70	60	62.45	131.0	95.4	110	52

	[1] 1 hr.	240	150	6.9	11.99	10.8	74	23	60	38.8	118.5	71.6	212	120
	[1] 1 hr.	240	150	7.74	14.9	12.7	93	30	60	66.9	73.0	67.0	9	98
	[1] 30 min.	240	150	7.7	16.25	14.3	111	23	60	23.8	42.1	35.7	77	35
	15 min.	120	120						30	11.3	52.5	21.3	365	75
	Average			3.4	5.96	4.9	75	41		29.0	58.3	40.4	101	62
B	3 hr.	240	120	1.4	1.53	1.47	9	46	30	16.4	39.0	33.0	137	20
	1 hr. 15 min.	240	150	1.15	1.75	1.53	52	36	60	32.7	71.3	53.1	118	47
	1 hr. 30 min.	240	120	2.95	3.24	2.96	10	96	60	23.8	29.1	23.8	22	100
	7 min.	240	120	0.34	0.38	0.36	12	50	30	25.7	33.0	27.9	28	69
	1 hr. 30 min.	240	120	1.79	2.3	2.1	10	39	60					
	2 hr.	240	120	1.15	1.61	1.41	40	42	30					
	10 min.	240	120	1.15	1.47	1.37	27	31	60					
	Average			1.4	1.75	1.6	25	42		24.6	43.1	34.5	75	46

[1] Both splanchnic nerves cut before fatigue.

the continuous line that of the normal muscle expressed in β units. The threshold of the nerve-muscle is magnified ten times. In Fig. 3 the threshold (at 2) was taken after the muscle was fatigued through its nerve for one hour, pulling 120 times a minute against a spring having an initial tension of 120 gm. At the end of this period of fatigue the preparation rested five minutes and then a reading was taken (at 3). The left splanchnic nerves were stimulated for 30 seconds, and after a wait of three minutes the thresholds were taken again (at 4). The threshold of the muscle decreased from 70.2 to 43.7 β units, a recovery of 69 per cent, and from 1.65 to 1.12 β units, a recovery of 96 per cent, in the nerve-muscle. This shows clearly that the adrenalin secreted, or the increase in blood pressure, or the two together lowered the fatigue threshold.

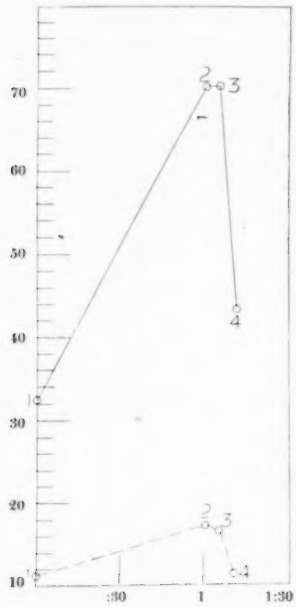

FIGURE 3. — A curve plotted from the data of one experiment. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the muscle, the broken line that of the nerve-muscle. The curve of the nerve-muscle is magnified ten times, that of the muscle is normal.

(1) Normal threshold stimulus. (2) The threshold after fatiguing the muscle for one hour. The muscle contracted 120 times per minute against a spring having an initial tension of 120 gm. (3) The threshold after five minutes' rest. (4) The threshold three minutes after the left splanchnic nerves were stimulated for 30 seconds.

That the action of adrenalin in reducing the fatigue threshold is not dependent upon an increase in blood pressure is evident, since the amount of adrenalin given has been shown by Cannon and Lyman [1] to produce a fall in arterial pressure.

To determine the effect of increased arterial pressure alone the adrenal glands (in some cases only the left)[2] were ligated and, after a period of fatigue of the

[1] CANNON and LYMAN: this Journal, 1912–13, xxxi, p. 376.

[2] According to Elliott, the innervation of the adrenal glands is homolateral. ELLIOTT: Journal of physiology, 1912, xliv, pp. 374–409.

muscle, the left splanchnic nerves were stimulated as in the experiment represented in Fig. 3. Four experiments were performed in which seven readings of the nerve-muscle and four of the muscle were taken. In these the average normal threshold of 1.4 β units for the nerve-muscle was increased by fatigue to 1.75 β units, an increase of 25 per cent. The threshold of the muscle was increased by fatigue from 24.6 to 43.1 β units, 75 per cent. The splanchnic nerves were then stimulated as described above. The average fatigue threshold in the nerve-muscle was decreased by this stimulation from 1.75 to 1.6 β units, a recovery of 42 per cent, and in the muscle from 43.1 to 34.5 β units, a recovery of 46 per cent. (See Table II, *B*.) The blood pressure in the majority of cases was increased more than 40 mm. of mercury. The original pressure in most cases was about 90 to 100 mm. of mercury as compared to 110 and 130 mm. in the animals in which the adrenal glands were intact. Evidently, therefore, increased blood pressure can in itself largely restore these fatigued structures to normal irritability.

The Fatigue Threshold of a Denervated Muscle as Affected by Adrenalin.

The results obtained on the denervated muscles were not quite as consistent as those on the normal muscle. In two experiments in which the left peroneus communis had been cut 6 and 7 days, adrenalin had no effect upon the fatigue threshold. Six later experiments were performed on animals in which the left peroneus communis nerve had been cut 7, 8, 12, 14, 15, and 16 days. In these, positive results were obtained and the recovery of the threshold by adrenalin was from 6 to 100 per cent. The average normal threshold for the six experiments, in which adrenalin was used to increase the fatigue irritability, was 47.8 β units. This was increased by fatigue to 138.8, an increase of 190 per cent. After an injection of adrenalin (0.1 to 0.5 cc.) this fatigue threshold was decreased to 102.9 β units, a recovery of 39 per cent.

Fig. 4 is a curve plotted from the data of one of the experiments performed to show the effect of small doses of adrenalin on the fatigue threshold of a denervated muscle. In this animal 2 cm. of the peroneus communis nerve were removed 7 days previous to

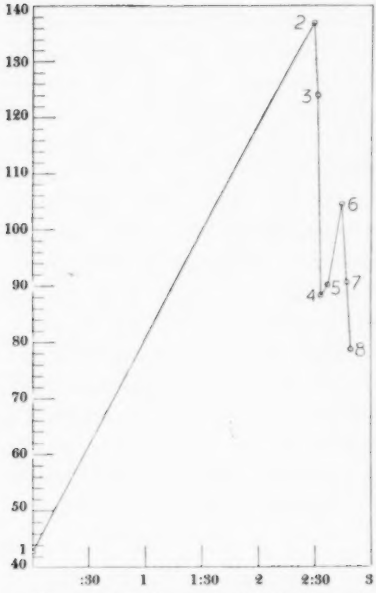

FIGURE 4. — A curve plotted from the data of one experiment performed on a denervated muscle. The peroneus communis nerve was cut seven days before this experiment was performed. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate.

(1) Normal threshold of muscle. (2) The threshold after the muscle was fatigued for two hours and thirty minutes. The muscle contracted 240 times a minute against a spring having an initial tension of 120 gm. (3) The threshold two minutes after an injection of adrenalin (0.5 cc. of a 1:100,000 solution). (4) Threshold taken one minute after (3). (5 and 6) Rests of four and eight minutes respectively. (7) Threshold two minutes after an injection of adrenalin (0.5 cc. of a 1:100,000 solution). (8) Threshold two minutes after (7).

the experiment. Similar results were obtained from animals in which the nerve was cut 9, 12, 14, 15, and 16 days. In all cases strong faradic stimulation of the distal end of the cut nerve gave no muscular response. In this figure (at 2) the threshold was taken after the muscle was fatigued for two hours and thirty minutes. The muscle contracted 240 times per minute against a spring having an initial tension of 120 gm. Through a cannula placed in the left external jugular vein 0.5 cc. of adrenalin was injected and two minutes later, with blood pressure slightly below the original level, the threshold reading (at 3) showed a recovery of 13 per cent, from 137.5 to 124.5 β units. One minute later, or three minutes after the injection, with blood pressure restored to the original level, the threshold (at 4) was decreased to 89.0 β units, a recovery of 51 per cent. After four more minutes the threshold (at 5) was 91.4 β units, and eight minutes later (at 6) 105 β units. At this point another 0.5 cc. adrenalin was injected intravenously, and after two minutes, with blood pressure restored, the threshold was reduced from 105 to 91.8 β units, a recovery of 48 per cent (at 7). Four minutes after the injection the threshold (at 8) dropped to 79.2 β units, a recovery of 61 per cent.

The lowering of the threshold stimulus in the denervated as well as in the fatigued normal muscle must be due to the action of adrenalin. In this case, however, the threshold did not remain lowered after the injection.

The question may arise as to whether or not the time allowed was sufficient for degeneration of the nerves. Howell and Huber found that seven days after the ulnar nerves of dogs were cut complete degeneration resulted and that partial irritability returned on the twenty-first day.[1] Huber found also that the nerve-endings in the interosseus muscle of the rabbit degenerated in from two to six days.[2] According to Bethe, seven to nine days are required in dogs and three to five days in rabbits for the nerve-endings to degenerate.[3] Tucket claims that the hypolemmal fibres of the flexor profundis muscle of the pigeon degenerate in two days or less.[4] Although there is considerable variation in the time required for degeneration of nerves in different animals and even in the different nerves of the same animal, it seems quite improbable that the peroneus communis nerve in the cat would require a longer time than the ulnar in the dog. Moreover, a marked similarity was found in the threshold stimuli of the denervated and curarized muscles. The average threshold stimulus for the 14 denervated animals was found to be 62.5 β units, and that for 14 curarized animals, in which there was complete immobility, was 63.5 β units. From these results there is little doubt that the nerve-endings of the denervated muscle were functionless. The nerves, moreover, were always tested with a strong faradic current before each experiment and were invariably found inactive.

Does Adrenalin Act by Bettering the Circulation?

The suggestion that adrenalin does not produce its beneficial effects on a fatigued muscle by bettering the circulation is made

[1] Howell and Huber: Journal of physiology, 1892, xiii, p. 358.

[2] Huber: this Journal, 1900, iii, p. 341.

[3] Bethe: Allgemeine Anatomie und Physiologie des Nervensystems, Leipzig, 1903, p. 162.

[4] Tucket: Reviewed by Langley in the Proceedings of the Royal Society of London, 1906, B, 78, p. 179.

by Cannon and Nice, who offer the following evidence[1]: "Against this supposition is the observation that when the arteries are deprived of their central innervation, as was the case with the arteries supplying the contracting muscle, adrenalin causes not a dilation but a constriction of the vessels.[2] And even if adrenalin did not cause vasoconstriction in this region, it could hardly produce much further dilation, for, as already noted, the vascular nerves had been cut and furthermore were being stimulated at a rate favorable to relaxation."

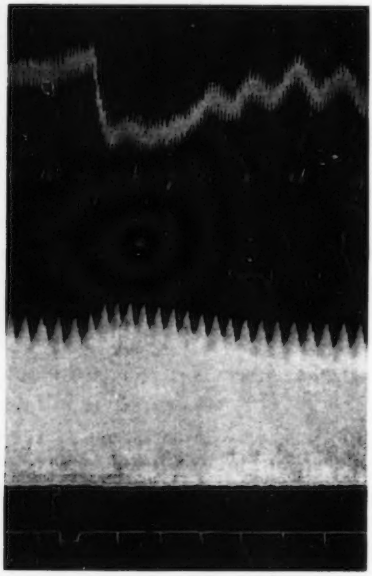

FIGURE 5. — Top record, blood pressure with mercury manometer. Middle record, contractions of the tibialis anticus muscle 240 times per minute against a spring with an initial tension of 120 gm. Bottom record (zero blood pressure) injection of 0.4 cc. of adrenalin (1:100,000). Time in half minutes.

Working upon this supposition, it was deemed advisable to make a comparative study of adrenalin and amylnitrite, since both may act as peripheral dilators.

Figs. 5 and 6 are curves obtained from the left tibialis anticus muscle. The rate of stimulation was 240 times a minute. The muscle in Fig. 5 contracted against a spring having an initial tension of 120 gm. and that in Fig. 6 having an initial tension of 100 gm. In Fig. 5 the muscle was after-loaded and in Fig. 6 it was loaded. The muscle lever magnified the contractions 4.4 times. In Fig. 5, at the point indicated on the base line, 0.4 cc. of adrenalin (1:100,000) was injected into the left external jugular vein. There resulted a fall of 25 mm. of mercury in the arterial

[1] CANNON and NICE: *Loc. cit.*, p. 55.

[2] CANNON and LYMAN: this Journal, 1913, xxxi, p. 376.

pressure and a concurrent betterment of 15 per cent in the height of contraction, requiring two minutes and fifteen seconds of fatigue before it returned to the former level. In Fig. 6, at the point indicated by an arrow, a solution of amylnitrite was injected into the right external jugular vein. There resulted a fall of 70 mm. of mercury in arterial pressure and a betterment of 4.1 per cent in the height of muscular contraction, requiring fifteen seconds of fatigue to decrease the height of contraction to its former level. In neither case did the blood pressure fall below the critical region.[1]

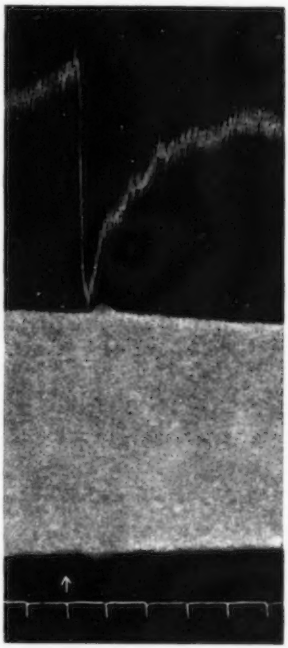

FIGURE 6.—Top record, blood pressure with mercury manometer. Middle record, contractions of tibialis anticus muscle 240 per minute against a spring with an initial tension of 100 gm. direct load. Bottom record (zero blood pressure) time in half minutes. The arrow indicates the point at which a solution of amylnitrite was injected.

Although the fall in arterial pressure caused by dilation of the vessels due to amylnitrite was almost three times as great as that produced by the adrenalin, yet the resultant betterment was only about one-fourth the percentage height and lasted but one-ninth the time. The fact that the decrease in blood pressure caused by adrenalin cannot in itself account for the bettering effect upon the muscle curve has been shown by Cannon and Nice and myself.[2] In all cases in which these solutions caused an equal fall in arterial pressure, adren-

[1] In some cases with amylnitrite the normal blood pressure, which was high, dropped sharply and fell below the critical region. GRUBER: this Journal, 1913, xxxii, p. 221. There resulted an increase in muscular contraction due to the betterment in circulation caused by the dilation of the vessels before the critical region was reached. During the time that the pressure was below the critical region the muscle contraction fell. As the blood pressure again rose to normal the muscle contraction increased similarly.

[2] CANNON and NICE: *Loc. cit.*, p. 55; GRUBER: *Loc. cit.*, p. 226.

alin caused a betterment in the height of contraction, while amylnitrite caused no appreciable change.

Still other results were obtained in which adrenalin caused no change in mean blood pressure but an increase in pulse pressure, with a resultant increase in the contraction. I found, as did Cannon and Nice, that the first increase in the arterial pressure during splanchnic stimulation is caused by the contraction of the

FIGURE 7.—Top record, contractions of tibialis anticus muscle 64 per minute against a spring having an initial tension of 120 gm. Bottom record, the time in half minutes. At the points indicated by arrows 0.5 cc. of adrenalin (1:1,000,000) was injected into the tube leading from the pressure bottle. The irrigation pressure was 95 mm. of mercury.

arteries in the splanchnic area.[1] This brings about a betterment in the height of muscular contraction, the period of which is very short.

It was found possible to prevent an increase of blood pressure during splanchnic stimulation by pulling on a fine cord looped about the aorta whenever the blood pressure showed a tendency to rise. Maintaining an even blood pressure did not, however, prevent a second prolonged rise, which followed immediately upon the first in every case. The second rise must be due to the secretion of adrenalin during splanchnic stimulation.

Fig. 7 is offered as further evidence that adrenalin does not act by bettering the circulation or by liberation of sugar from the liver. Here the hind leg was irrigated as previously described (see

[1] CANNON and NICE: *Loc. cit.*, p. 48.

p. 337). In this record the left tibialis anticus muscle contracted 64 times a minute against a spring having an initial tension of 120 gms. The magnification of the contraction by the lever is 4.4 times. At the point indicated by the arrow 0.5 cc. of adrenalin (1:1,000,000) was injected into the running solution close to the cannula in the artery. There was a betterment of 2.8 per cent in the height of muscular contraction, which required thirty seconds of fatigue to restore it to the original slope of the curve. In every case the stream leading from the iliac vein ran more slowly after the injection, a fact which would indicate vasoconstriction of the vessels rather than vasodilation. Similar results were obtained when doses of 0.5 cc. of a 1:100,000 or of a 1:5,000,000 solution were injected. The strength of these solutions of adrenalin was much stronger than that produced in an animal by an injection of 0.1 cc. of a 1:100,000 solution into the jugular vein. In the latter case the dilution by the blood and tissue fluids would be approximately 1:200,000,000 when the adrenalin reached the fatigued muscle.

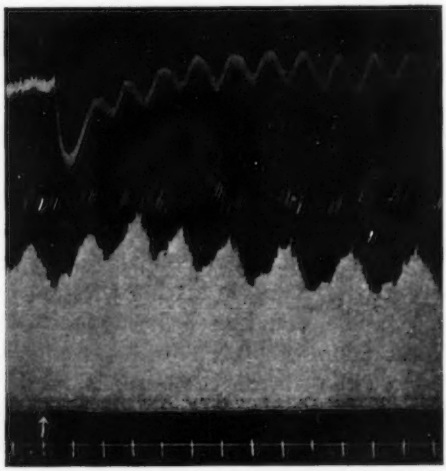

FIGURE 8. — Top record, blood pressure with mercury manometer. Middle record, contractions of a denervated muscle (tibialis anticus) 240 per minute against a spring having an initial tension of 120 gm. (peroneus communis nerve was cut nine days before this record was taken). Bottom record (zero blood pressure) time in half minutes. At the point indicated by an arrow 0.1 cc. of adrenalin (1:100,000) was injected intravenously.

IS THE ACTION OF ADRENALIN MUSCULAR OR NEURO-MUSCULAR?

Radwánska and Panella report that adrenalin acts either on the nerve trunk or on the neuro-muscular junction.[1] Oliver and

[1] RADWÁNSKA: *Loc. cit.*, pp. 728–736; PANELLA: Archives italiennes de biologie, 1907, xlvii, p. 30.

Schäfer and Dessy and Grandis report an effect on the muscle tissue itself.[1] That adrenalin lowers the fatigue threshold of a denervated muscle (7–16 days' degeneration) is cited in Fig. 4. Fig. 8 shows that it affects the height of muscular contraction. In this experiment the left tibialis anticus muscle was stimulated directly by thrusting platinum needle electrodes into it. The peroneus communis nerve supplying the muscle had been cut and 2 cm. removed nine days previous to the experiment. The rate of stimulation was 120 times per minute and the initial tension of the spring about 120 gms. The curve is magnified 4.4 times by the muscle lever. An injection of 0.1 cc. of adrenalin (1:100,000) was made into the left external jugular vein at the point indicated by an arrow. A fall in arterial pressure from 110 to 86 mm. of mercury and a simultaneous betterment of 20 per cent in the height of contraction were obtained. It required four minutes' fatigue to restore the muscle curve to its former level. Results similar to this were obtained from animals in which the nerve had been cut 7, 9, 12, 14, and 21 days. In all instances the nerve was inexcitable to strong faradic stimulation.

Discussion

From the above evidence one might infer that adrenalin acts primarily either on muscle substance or on the fatigue products. Dessy and Grandis concluded that adrenalin in some way neutralizes the fatigue products.[2] Albanese found in frogs and rabbits that, after the removal of the suprarenal capsules, these animals were prone to fatigue.[3] He therefore concluded that the function of the adrenal glands was to destroy or at least to transform the toxic substances, which as a result of muscular or nervous work are produced in the organism. Abelous and Langlois offered evidence that the suprarenal capsules in frogs and guinea pigs can modify, neutralize, or destroy poisons produced in the course of

[1] Oliver and Schäfer: *Loc. cit.*, p. 263; Dessy and Grandis: *Loc. cit.*, p. 231.

[2] Dessy and Grandis: *Loc. cit.*, p. 231.

[3] Albanese: Archives italiennes de biologie, 1892, xvii, p. 239.

muscular work, which accumulate in the organism after the destruction of the adrenal glands.[1]

Carrot and Josserand noted the influence of adrenalin on the blood pressure record before and after fatigue; 0.025 mg. of adrenalin per kilo injected in the femoral vein caused a rise of 10 cm. of mercury.[2] If injected into the femoral artery (leg at rest) the blood pressure was increased only 2 to 3 cm. of mercury. In the other femoral artery (leg tetanized for one-fourth hour) 0.055 mg. caused an elevation of only 1.5 cm. They claim that the adrenalin in the latter is neutralized by the fatigue products. Joteyko thinks that the chemical activity of adrenalin plays a role antagonistic to fatigue, and concludes, therefore, that it is a sarcoplasmic excitant.[3]

All these authors come to the conclusion that adrenalin produces its beneficial effects by neutralization, transformation, or destruction of the metabolites. It is quite true that all the phenomena shown in this paper can be explained on this assumption. It is contrary, however, to the conclusions of Radwánska, Panella, Cannon and Nice, and to results which I have obtained in experiments on the antagonism of adrenalin to curare which I shall soon publish.[4]

In Radwánska's experiments the muscle was stimulated with the nerve-endings intact. It seems, therefore, reasonable to suppose that in all cases he was stimulating nerve tissue. Since a muscle is more irritable when stimulated through its nerve than when stimulated directly (nerve and muscle), a slight change in the irritability of the muscle by adrenalin would naturally result in a greater contraction when the nerve was stimulated. The betterment in the results thus obtained, by stimulating the nerve directly, would be in proportion to the increase in irritability of the nerve over the muscle.[5]

[1] Abelous and Langlois: Archives de physiologie, 1892, xxiv, pp. 269–278. *Ibid.*, pp. 465–476.

[2] Carrot and Josserand: Comptes rendus, Société de Biologie, 1903, p. 51.

[3] Joteyko: Journal médical de Bruxelles, 1903, viii, p. 421.

[4] Radwánska: *Loc. cit.*, p. 728; Panella: *Loc. cit.*, p. 30; Cannon and Nice: *Loc. cit.*, p. 49.

[5] Gruber: this Journal, 1913, xxxii, p. 438. Figs. 1, 2, and 3 and Tables I and II of this article.

Panella's results can be interpreted to show that adrenalin is muscular in effect. Langley has demonstrated that nicotine and curare act upon a hypothetical "receptive substance." Since adrenalin has an action antagonistic to curare, adrenalin may be assumed also to act upon this substance.[1]

It is quite conclusive that adrenalin, in some way, causes a rapid recovery of the normal irritability of muscle after fatigue, and thus a betterment in the height of contraction. The question whether this is done by neutralizing, transforming, or destroying the fatigue toxins is still obscure. That the action may be on the muscle itself has been definitely shown in this paper; its effect, however, upon the nervous elements or on the region of the neuro-muscular union, cannot be denied.[2]

Summary

1. Adrenalin injected in small doses causes a recovery of the threshold irritability of the fatigued tibialis anticus muscle whether tested on the muscle or on the nerve-muscle.

2. Adrenalin acts quickly, requiring five minutes or less to produce its effect on the threshold. In that length of time, in some cases, it reduces the threshold to normal, whereas rest would require fifteen minutes to two hours.

3. Splanchnic stimulation causes, after fatigue, a quick recovery of the former threshold irritability. When the adrenal glands are tied off and the left splanchnic nerves stimulated there is also some recovery from the fatigue threshold of the nerve-muscle and of the muscle. This partial recovery is best accounted for as due to the increased blood pressure and improved circulation.

4. Adrenalin injected in small doses causes a recovery from the fatigue threshold of a denervated muscle (peroneus communis nerve cut six to sixteen days previous to the experiment).

[1] Langley: Proceedings of the Royal Society of London, 1906, lxxviii, B, p. 181. Journal of physiology, 1905–06, xxxiii, pp. 374–413.

[2] Oliver and Schäfer's betterment *Loc. cit.*, in muscular contraction may be accounted for in these ways: (1) storing up of adrenalin in the muscle, and (2) a small amount of fatigue before the muscles were excised, which was overcome in the muscle through which the adrenalin was allowed to pass.

5. Amylnitrite causes an increased height of muscular contraction simultaneously with a fall of blood pressure, due probably to vasodilation in the stimulated muscle and consequent betterment in circulation. This increase is small and of short duration. It occurs only when the fall in pressure is sharp and not below the critical region. If below this region there may be a brief betterment followed by a decrease in the height of contraction.

6. Adrenalin causes a betterment in contraction not wholly by vasodilation, as does amylnitrite, but specifically by action on the tissues or fatigue products. The betterment from adrenalin is prolonged and may occur even though no change in arterial pressure is brought about.

7. Adrenalin increases the height of contraction in an irrigated fatigued muscle when injected into the irrigating solution.

8. Adrenalin exerts an action on denervated muscle as well as on normal muscles. The percentage increase in the height of contraction here may be as great as in the normal muscles.

I wish to express my thanks to Dr. W. B. Cannon and to Dr. E. G. Martin for valuable suggestions offered me during these experiments.

THE EMERGENCY FUNCTION OF THE ADRENAL MEDULLA IN PAIN AND THE MAJOR EMOTIONS

By W. B. CANNON

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LIKE other endosecretory glands the adrenals have been studied by removing them and by injecting their extracts. Injection experiments have shown that the substance produced by the adrenal medulla (adrenin, adrenalin, epinephrin, etc.) is capable of producing many profound bodily changes. The most important of these changes are: a cessation of the activities of the alimentary canal; a notable shifting of the circulation from the great vessels of the abdomen to the lungs, heart, limbs and central nervous system; an increased cardiac vigor; and an augmentation of the sugar content of the blood. Little attention has been paid to the important question of the possible value of these striking bodily alterations as they might occur in the natural life of animals. It is significant that these effects are caused also by nervous discharges along sympathetic pathways — the discharges that are sent forth in crises of pain and great emotion. During the past three years, in a series of investigations conducted in this laboratory,[1] we have attempted to gain insight into the meaning of the changes wrought by adrenalin or increased adrenal secretion, and in this paper I propose to discuss the bearings of our results.

Adrenalin is Liberated Normally in Fear, Rage, Asphyxia and Pain

A point of prime importance in the functioning of the adrenal medulla is its subjection to central nervous influences coming to it by way of the splanchnics. With a variety of methods, in the

[1] CANNON and DE LA PAZ: this Journal, 1911, xxviii, p. 64. CANNON and HOSKINS: *ibid.*, 1911, xxix, p. 274. CANNON, SHOHL and WRIGHT: *ibid.*, 1911, xxix, p. 280. CANNON and LYMAN: *ibid.*, 1913, xxxi, p. 376. CANNON and NICE: *ibid.*, 1913, xxxii, p. 44. GRUBER: *ibid.*, 1913, xxxii, pp. 221, 438; and 1914, xxxiii, p. 335.

hands of various investigators,[1] proof has been brought that artificial stimulation of the splanchnic nerves will induce secretory activity in the adrenal medulla, and that in consequence adrenalin is increased in the blood. Thus the fact is now securely established that there exists in the body a mechanism by which this endosecretory gland can be made to discharge its products promptly into the circulation.

The question whether the medulla is stimulated to activity by nervous impulses aroused by the natural events in the course of an animal's life was taken up by de la Paz and me about three years ago.[2] We found that when a cat was frightened by a barking dog the blood in the cat's vena cava close in front of the opening of the adrenal veins gave definite evidence of the presence of adrenalin (relaxation of the rhythmically contracting intestinal strip), whereas blood from the same region previous to the excitement was ineffective. Later Hoskins and I found that strong stimulation of the sciatic nerve in an anaesthetized animal—such stimulation as would cause severe pain if the animal were not anaesthetized — and also asphyxia, resulted in greater activity of the adrenal medulla, as indicated by the increased amount of adrenalin in the cava blood.[3]

Our observation on asphyxia has been supported by Borberg and Fridericia,[4] and also by Starkenstein,[5] who found that an increase of CO_2 in the blood lessens the chromaffine substance in the adrenal medulla. And recently Czubalski also has inferred, from the rise of blood-pressure in asphyxia when the adrenals are intact and the absence of the rise if the adrenals are removed, that asphyxia sets free adrenalin in the blood.[6]

[1] *See* DREYER: this Journal, 1898–99, ii, p. 219. TSCHEBOKSAROFF: Archiv für die gesammte Physiologie, 1910, cxxxvii, p. 103. ASHER: Zentralblatt für Physiologie, 1910, xxiv, p. 927. KAHN: Archiv für die gesammte Physiologie, 1911, cxl, p. 240. MELTZER and JOSEPH: this Journal, 1912, xxix, p. xxxiv. ELLIOTT: Journal of physiology, 1912, xliv, p. 400. CANNON and LYMAN: *Loc. cit.*, p. 377; and others.

[2] CANNON and DE LA PAZ: *Loc. cit.*, p. 67.

[3] CANNON and HOSKINS: *Loc. cit.*, p. 278.

[4] BORBERG: Skandinavisches Archiv für Physiologie, 1913, xxviii, p. 125.

[5] STARKENSTEIN: Zeitschrift für experimentelle Pathologie und Therapie, 1911, x, p. 95.

[6] CZUBALSKI: Zentralblatt für Physiologie, 1913, xxvii, p.580.

Our observations on fear and pain have been supported by Elliott's study of the adrenalin content of the glands as affected by experimental procedures. He found that "fright," induced in cats by morphia or by β-tetrahydronaphthylamine, exhausts the glands, and that excitation of afferent nerves, such as the great sciatic, also causes adrenalin to disappear.[1] These results are what could be reasonably expected, for major emotions, as fear and rage, and such sensory stimulation as in a conscious animal would be painful are known to be accompanied by nerve impulses passing out via sympathetic fibres — impulses causing dilatation of the pupils, inhibition of gastric katastalsis and secretion, and contraction of arterioles.[2] And, as previously stated, the adrenal medulla has been proved to manifest increased secretory activity when affected by nerve impulses coming via these same pathways.

Blood Sugar is Increased in Fear, Rage, Asphyxia and Pain if the Adrenals are Intact

Artificial stimulation of splanchnic nerves not only liberates adrenalin but also releases sugar from the liver.[3] If, however, the adrenals are removed from the body, splanchnic stimulation will not evoke glycosuria.[4] The participation of the adrenal medulla, therefore, seems to be essential for the mobilization of sugar in the blood, when that is accomplished by nerve impulses.

As pointed out above, adrenal secretion is increased in major emotional states, in asphyxia, and on stimulation of nerves for pain; hyperglycaemia is the normal accompaniment of such experimental nervous stimulations as evoke an increased adrenal secretion; therefore, that fear and rage, pain and asphyxia would give rise to hyperglycaemia might reasonably be expected.

[1] ELLIOTT: *Loc. cit.*, p. 409.

[2] *See* CANNON: The Mechanical Factors of Digestion, London and New York, 1911, p. 217; also American journal of the medical sciences, 1909, cxxxvii, p. 480.

[3] *See* MACLEOD: Diabetes: its Pathological Physiology, London, 1913, pp. 61–62.

[4] *See* GAUTRELET and THOMAS: Comptes rendus de la Société de Biologie, 1909, lxvii, p. 233. MACLEOD: Proceedings of the Society for Experimental Biology and Medicine, 1911, viii, p. 110.

The influence of asphyxia as a highly potent condition for the mobilization of sugar in the blood is well established.[1] Starkenstein has shown, however, that asphyxia due to carbon monoxide poisoning is not accompanied by hyperglycaemia if the adrenal glands have been removed.[2]

That experimental procedures attended by pain result in the appearance of sugar in the urine was demonstrated many years ago by Böhm and Hoffman.[3] Their observations on cats have proved true also of rabbits;[4] and recently it has been shown that an operation involving some pain increases blood sugar in dogs.[5]

That pure emotional excitement — fear or rage — will have the same effect was proved when Shohl, Wright and I obtained glycosuria in cats by fastening them to a comfortable holder or by placing them in small cages and permitting a dog to bark at them. Whether glycosuria appeared promptly or not depended on the animal's emotional reaction to its experience. Neither pain, cooling nor being bound, therefore, was a factor in the result — the essential element was the fright or rage of the animal.[6] Our conclusion has been confirmed by one of my former students, Dr. W. G. Smillie, who found that 4 of 9 medical students (all normally aglycosuric) had glycosuria after a hard examination, and only 1 of the 9 had glycosuria after an easier examination.[7] Also Rolly and Opper-

[1] For evidence and for reference to literature, *see* BANG: Der Blutzucker, Wiesbaden, 1913, pp. 104–108.

[2] STARKENSTEIN: *Loc. cit.*, p. 94. He was able to produce glycosuria in the absence of the adrenals by strong stimulation of the central end of the cut vagus; he therefore concluded that the sympathetic impulses are primary and that the adrenals are accessory in evoking glycogenolysis.

[3] BÖHM and HOFFMAN: Archiv für experimentelle Pathologie und Pharmakologie, 1878, viii, p. 295.

[4] ECKHARD: Zeitschrift für Biologie, 1903, xliv, p. 408.

[5] LOEWY and ROSENBERG: Biochemische Zeitschrift, 1913, lvi, p. 114.

[6] CANNON, SHOHL and WRIGHT: *Loc. cit.*, p. 283.

[7] The tests, which were positive with Fehling's solution, Nylander's reagent, and also with phenyl-hydrazine, were made on the first urine passed after the examination. Mr. C. H. Fiske and I have found sugar in the urine in 12 of 25 members of the Harvard University foot-ball squad, immediately after the final and most exciting contest of the season. Five of the positive cases were substitutes who were not called upon to enter the game. The only spectator whose urine was examined had a marked glycosuria.

mann, Jacobsen, and Hirsch and Reinbach have recently reported that the mere handling of a rabbit preparatory to operating on it will increase the blood sugar (in some cases from .10 to .23 and .27 per cent) and may result in glycosuria.[1] Indeed, the readiness with which this response occurs has been pointed out as a source of error in estimates of the "normal" sugar content of the blood.

In our studies[2] we observed that animals which had glycosuria when bound for about an hour, failed to have it after careful adrenalectomy, although bound between two and three times as long as before, and although still manifesting the same degree of excitement which they had manifested previous to the operation. This result harmonizes with that already reported that the presence of the adrenals is necessary when hyperglycaemia is to be produced by splanchnic stimulation.

Fear, rage, asphyxia and pain, therefore, are accompanied by an increased discharge of adrenalin into the blood, and by a freeing of stored glycogen from the liver for circulation through the body as glucose. The hyperglycaemia and the adrenalinaemia are both due to nervous discharges. Since, in the absence of the adrenals, nerve impulses fail to evoke sugar; and since, in the absence of nerve impulses, a sufficient injection of adrenalin will evoke sugar, the inference seems justified that, for the ready increase of blood sugar by nervous discharges in emotions, circulating adrenalin must be simultaneously increased. What explanation can be offered for this remarkable outpouring from the adrenal medulla and the concomitant glycogenolysis that floods the body with sugar?

The Reflex Nature of Bodily Responses to Pain and the Major Emotions

The most significant feature of these bodily reactions to pain and to emotion-provoking objects is that they are of the nature of reflexes, — they are not willed movements, indeed they are often distressingly beyond the control of the will. The pattern of the

[1] ROLLY and OPPERMANN: Biochemische Zeitschrift, 1913, xlix, p. 201. JACOBSEN: *ibid.*, 1913, li, p. 449. HIRSCH and REINBACH: Zeitschrift für physiologische Chemie, 1913, lxxxvii, p. 122.

[2] CANNON, SHOHL and WRIGHT: *Loc. cit.*, p. 285.

reaction, in these as in other reflexes, is deeply inwrought in the workings of the nervous system, and when the appropriate occasion arises, typical organic responses are evoked through inherent automatisms.

It has long been recognized that the most characteristic feature of reflexes is their "purposive" nature, or their utility either in preserving the welfare of the organism or in safeguarding it against injury. The reflexes of sucking, swallowing, vomiting and coughing, for instance, need only to be mentioned to indicate the variety of ways in which reflexes favor the continuance of existence. When, therefore, these automatic responses accompanying pain and fear and rage — the increased discharge of adrenalin and sugar — are under consideration, it is reasonable to enquire first as to their utility.

Numerous ingenious suggestions have been offered to account for the more obvious changes accompanying emotional states — as, for example, the bristling of the hair and the uncovering of the teeth in an access of rage.[1] The most widely applicable explanation proposed for these spontaneous reactions is that during the long course of racial experience they have been developed for quick service in the struggle for existence. McDougall has suggested that an association has become established between peculiar emotions and these ingrained native reactions; thus the emotion of fear is associated with the instinct for flight, and the emotion of anger or rage with the instinct for fighting or attack.[2] Crile likewise has emphasized the importance of adaptation and natural selection, operative through age-long racial experience, in enabling us to account for the already channelled responses which we find established in our nervous organization. And on a principle of "phylogenetic association" he assumes that fear, born of innumerable injuries in the course of evolution, has developed into portentous foreshadowing of possible injury and has become, therefore, capable of arousing in the body all the offensive and defensive activities that favor the survival of the organism.[3]

[1] *See* DARWIN: Expression of Emotions in Man and Animals, New York, 1905, pp. 101, 117.

[2] MCDOUGALL: Introduction to Social Psychology, London, 1908, pp. 49, 59.

[3] CRILE: Boston medical and surgical journal, 1910, clxiii, p. 893.

Because the adrenalinaemia and the hyperglycaemia following painful or strong emotional experiences are reflex in character, and because reflexes as a rule are useful responses, we are justified in the assumption that under these circumstances the increase of adrenalin and sugar in the blood is useful. What then is the possible value of these reactions?

The Utility of Sugar and Adrenalin Liberated in Pain and the Major Emotions

That the outpouring of adrenalin and sugar in conditions of pain and the major emotions has value for the organism was the leading idea in the researches recently reported from this laboratory.[1] In order that these reactions may be useful they must be *prompt*. Such is the case. Some unpublished observations made in this laboratory show that the latent period of adrenal secretion, when the splanchnic nerve is stimulated below the diaphragm, is not longer than 16 seconds; and Macleod states that within a few minutes after splanchnic stimulation the sugar in the blood rises between 10 and 30 per cent.[2] The two secretions are, therefore, almost instantly ready for service.

Conceivably the two secretions might act in conjunction or each might have its own function alone. Thus adrenalin might serve in co-operation with nervous excitement to produce hyperglycaemia, or it might have that function and other functions quite apart from that. Before these possibilities are considered, however, the value of the hyperglycaemia itself will be discussed.

The Utility of Increased Blood Sugar. — In the paper on emotional glycosuria previously mentioned,[3] a clue was taken from McDougall's suggestion of a relation between "flight instinct" and "fear emotion," and "pugnacity instinct" and "anger emotion." And the point was made that, since the fear emotion and the anger emotion are, in wild life, likely to be followed by activities (running or fighting) which require contraction of great muscular masses in supreme and prolonged struggle, a mobilization of sugar

[1] *See* CANNON: Proceedings American Philosophical Society, 1911, l, p. 227.
[2] MACLEOD: Diabetes, etc., p. 80.
[3] CANNON, SHOHL and WRIGHT: *Loc. cit.*, p. 286.

in the blood might be of signal service to the laboring muscles. Pain — and fighting is almost certain to involve pain — would, if possible, call forth even greater muscular effort. "In the agony of pain almost every muscle of the body is brought into strong action," Darwin wrote, for "great pain urges all animals, and has urged them during endless generations, to make the most violent and diversified efforts to escape from the cause of suffering."[1]

That muscular work is performed by energy supplied in carbonaceous material is shown by the great increase of carbon-dioxide output in severe muscular work, which may exceed twenty times the output during rest. Furthermore, the storage of glycogen in muscle, and the disappearance of this glycogen deposit from excised muscle stimulated to activity,[2] or its reduction after excessive contractions produced by strychnine,[3] and the lessened ability of muscles to work if their glycogen store has been reduced,[4] and the simple chemical relation between sugar and the lactic acid which appears when muscles are repeatedly made to contract, are all indications that carbohydrate (sugar and glycogen) is the elective source of energy for contraction. This conclusion is supported in recent careful studies by Benedict and Cathcart, who have shown that a small but distinct increase in the respiratory quotient occurs during muscular work, and that a decrease in the quotient follows, thus pointing to a larger proportion of carbohydrate burned during muscular work than before or after — i.e., a call on the carbohydrate deposits of the body.[5]

[1] DARWIN: *Loc. cit.*, p. 72. It is recognized that both pain and the major emotions may have at times depressive rather than stimulating effects. Though severe pain may soon induce extreme prostration, the whip and spur illustrate its primary exciting action. And though fear may become the most depressing of all emotions, it acts at first as a powerful stimulus. "A man or animal driven through terror to desperation is endowed with wonderful strength, and is notoriously dangerous in the highest degree." (DARWIN: *Loc. cit.*, p. 81.)

[2] NASSE: Archiv für die gesammte Physiologie, 1869, ii, p. 106; 1877, xiv, p. 483.

[3] FRENTZEL: Archiv für die gesammte Physiologie, 1894, lvi, p. 280.

[4] ZUNTZ: Oppenheimer's Handbuch der Biochemie, Jena, 1911, iv (first half), p. 841.

[5] BENEDICT and CATHCART: Muscular Work, a metabolic study, Washington, 1913, pp. 85–87.

Whether circulating sugar can be immediately utilized by active muscles has been a subject of dispute. The claim of Chauveau and Kaufmann that a muscle uses about three and a half times as much blood sugar when active as when resting,[1] although supported by Quinquaud,[2] and by Morat and Dufourt,[3] has been denied by Pavy, who failed to find any difference between the sugar content of arterial and venous blood when the muscle was contracting;[4] and also by Magnus-Levy, who has estimated that the amount of change in sugar content of the blood passing through a muscle must be so slight as to be within the limits of the error of analysis.[5] On the other hand, when blood or Ringer's solution is repeatedly perfused through contracting heart muscle, the evidence is clear that the contained sugar may more or less completely disappear. Thus Locke and Rosenheim found that from 5 to 10 centigrams of dextrose disappeared from Ringer's solution repeatedly circulated through the rabbit heart for eight or nine hours.[6] And recently Patterson and Starling have shown that if blood is perfused repeatedly through a heart-lung preparation for three or four hours, and the heart is continually stimulated by adrenalin added to the blood, the sugar in the blood wholly vanishes; or if the supply of sugar is maintained, the consumption may rise as high as 8 mgms. per gram per hour — about four times the usual consumption.[7] When an animal is eviscerated it may be regarded as a preparation in which the muscles are perfused with their proper blood, pumped by the heart and oxygenated by the lungs. Under these circumstances, the percentage of sugar in the blood steadily falls,[8] because the utilization by the tissues is not

[1] Chauveau and Kaufmann: Comptes rendus, Académie des Sciences, 1886, ciii, p. 1062.

[2] Quinquaud: Comptes rendus, Société de Biologie, 1886, xxxviii, p. 410.

[3] Morat and Dufourt: Archives de physiologie, 1892, xxiv, p. 327.

[4] Pavy: The Physiology of the Carbohydrates, London, 1894, p. 166.

[5] Magnus-Levy: v. Noorden's Handbuch der Pathologie des Stoffwechsels, 1906, i, p. 385.

[6] Locke and Rosenheim: Journal of physiology, 1907, xxxvi, p. 211.

[7] Patterson and Starling: Journal of physiology, 1913, xlvii, p. 143.

[8] *See* Macleod and Pearce: this Journal, 1913, xxxii, p. 192. Pavy and Siau: Journal of physiology, 1903, xxix, p. 375. Macleod: this Journal, 1909, xxiii, p. 278.

compensated for by further supply from the liver. Thus, although there may be doubt that analyses of sugar in the blood flowing into and out from an active muscle during a brief period can be accurate enough to prove a clear difference, the evidence from the experiments above cited shows that when the supply of sugar is limited it disappears to a greater or less degree when passed repeatedly through muscular organs.

The argument may be advanced, of course, that the sugar which thus disappears is not directly utilized, but must first be changed to glycogen. There is little basis for this assumption. There is, however, considerable evidence that increasing blood sugar does, in fact, directly increase muscular efficiency. Thus Locke proved that if oxygenated salt solution is perfused through the rabbit heart, the beats begin to weaken after one or two hours; but if now 0.1 per cent dextrose is added to the perfusing fluid the beats at once become markedly stronger and may continue with very slow lessening of strength as long as seven hours.[1] And Schumberg noted that when he performed a large amount of general bodily work (thus using up blood sugar) and then tested flexion of the middle finger in an ergograph, the ability of the muscle was greater if he drank a sugar solution than if he drank an equally sweet solution of "dulcin." He did not know during the experiment which solution he was drinking.[2] These observations have been confirmed by Prantner and Stowasser, and by Frentzel.[3] In experiments on cats Lee and Harrold found that when sugar is removed from the animal by means of phlorhizin the tibialis anticus is quickly fatigued; but if, after the phlorhizin treatment, the animal is given an abundance of sugar and then submitted to the test, the muscle shows a much larger capacity for work.[4] All this evidence is, of course, favorable to the view that circulating sugar may be quickly utilized by contracting muscles.

From experimental results presented above it is clear that muscles work preferably by utilizing the energy stored in sugar, that great muscular labor is capable of considerably reducing the

[1] Locke: Centralblatt für Physiologie, 1900, xiv, p. 671.
[2] Schumberg: Archiv für Physiologie, 1896, p. 537.
[3] Frentzel: Archiv für Physiologie, 1899, Supplement Band, p. 145.
[4] Lee and Harrold: this Journal, 1900, iv, p. ix.

quantity of stored glycogen and of circulating sugar, and that under circumstances of a lessened sugar content the increase of blood sugar considerably augments the ability of muscles to continue contracting. The conclusion seems justified, therefore, that the hyperglycaemia attendant on the major emotions and pain would be of direct benefit to the organism in the strenuous muscular efforts involved in flight or conflict or struggle to be free.

The Utility of Increased Adrenalin in the Blood. — In early work on the effects of removal of the adrenal bodies, muscular weakness was not infrequently noted. In 1892 Albanese showed that muscles stimulated after adrenalectomy were much more exhausted than when stimulated the same length of time in the same animal before the removal.[1] Similarly Boinet reported that rats recently deprived of their adrenal glands were much more quickly exhausted in a revolving cage than were normal animals.[2] A beneficial effect of adrenal extract on fatigued muscle, even when applied to the solution in which the isolated muscle is contracting, was claimed by Dessy and Grandis, who studied the phenomenon in the salamander.[3]

It seemed possible, because of the early evidence that adrenalectomy has a debilitating effect on muscular power, and that injection of adrenal extract has an invigorating effect, that increased adrenal secretion, as a reflex result of pain or the major emotions, might not only be useful in helping to mobilize sugar, but also might act in itself as a dynamogenic factor in the performance of muscular work. On the basis of this possibility Nice and I tested the effect of stimulating the left splanchnic nerve (thus causing adrenal secretion), or injecting adrenalin, on the contraction of the fatigued tibialis anticus.[4] We found that when

[1] Albanese: Archives italiennes de biologie, 1892, xvii, p. 243.

[2] Boinet: Comptes rendus, Société de Biologie, 1895, xlvii, pp. 273, 498.

[3] Dessy and Grandis: Archives italiennes de biologie, 1904, xli, p. 231. Biedl's observation (*See* Biedl: Innere Sekretion, Second Edition, Leipzig, 1913, i, p. 376), that in selachians removal of the interrenal bodies (corresponding to the adrenal cortex) results in muscular weakness, might indicate that the cortex was directly involved in muscular efficiency, but the failure of the animals to take food after undergoing the operation renders that conclusion hazardous.

[4] Cannon and Nice: *Loc. cit.*, p. 54.

arterial pressure was of normal height, and was prevented from rising in the legs while the splanchnic was being stimulated, there was a distinct rise in the height of contraction of the fatigued muscle. We drew the inference that adrenalin set free in the blood may operate favorably to the organism by preparing fatigued muscles for better response to the nervous discharges sent forth in great excitement.

This inference has been further tested during the past summer by one of my students, Mr. C. M. Gruber, who has examined the effects of minute amounts of adrenalin (0.1 or 0.5 cc. of 1:100,000), and also of splanchnic stimulation, on the threshold stimulus of fatigued neuromuscular and muscular apparatus. Fatigue raises the threshold not uncommonly 100 or 200 per cent and in some instances as much as 600 per cent. Rest will restore the normal threshold in periods varying from 15 to 120 minutes, according to the length of previous stimulation. If a small dose of adrenalin is given, however, the normal threshold may be restored in 3 to 5 minutes.[1]

From the foregoing evidence the conclusion is warranted that adrenalin, when freely liberated in the blood, not only aids in bringing out sugar from the liver's store of glycogen, but also has a remarkable influence in quickly restoring to fatigued muscles, which have lost their original irritability, the same readiness for response which they had when fresh. Thus the adrenalin set free in pain and in fear and rage would put the muscles of the body unqualifiedly at the disposal of the nervous system; the difficulty which nerve impulses might have in calling the muscles into full activity would be practically abolished; and this provision, along with the abundance of energy-supplying sugar newly flushed into the blood, would give to the animal in which these mechanisms are most efficient the best possible conditions for putting forth supreme muscular efforts.[2]

Does Adrenalin Normally Secreted Inhibit the Use of Sugar

[1] *See* GRUBER: this Journal, 1914, xxxiii, p. 354.

[2] If these results of emotion and pain are not "worked off" by action, it is conceivable that the excessive adrenalin and sugar in the blood may have pathological effects (*Cf.* CANNON: Journal of the American Medical Association, 1911, lvi, p. 742).

by the Tissue? — The only evidence opposed to the conclusion which has just been drawn is that which may be found in results recently reported by Wilenko. He injected adrenalin into urethanized rabbits, usually 1 mgm. per kilo body weight, and then found that the animals did not oxidize any part of an intravenous injection of glucose. Rabbits supplied with glucose in a similar manner, but not given adrenalin, have an increased respiratory quotient. Wilenko concluded therefore that adrenalin lessens the capacity of the organism to burn carbohydrates.[1] In a later paper he reported that adrenalin when added to Locke's solution (with glucose), and perfused through the isolated rabbit heart, notably increases the use of sugar by the heart (from 2.2–2.8 to 2.9–4.3 mgm. glucose per gm. heart muscle per hour), but that the heart removed after the animal had received a subcutaneous injection of adrenalin uses much less sugar, only 0.5–1.2 mgm. per gm. per hour. From these results Wilenko concludes that adrenalin glycosuria is the result of the disturbance of the *use* of sugar — an effect which is not direct on the sugar-consuming organ, but indirect through action on some other organ.[2]

Wilenko's conclusion fails to account readily for the disappearance of glycogen from the liver in adrenalin glycosuria. Furthermore, Lusk has recently reported that the subcutaneous administration of adrenalin (1 mgm. per kilo body weight) to dogs, simultaneously with 50 grams of glucose by mouth, interferes not at all with the use of the sugar — the respiratory quotient remains for several hours at 1.0; i.e., at the figure which glucose alone would have given.[3] In other words Lusk's results with dogs are directly contradictory to Wilenko's results with rabbits. Nevertheless, Wilenko's conclusion might be quite true for the glycosuria produced by adrenalin alone (which must be excessive), and yet have no bearing whatever on the glycosuria produced physiologically by splanchnic stimulation, even though some adrenalin is thereby simultaneously liberated.

[1] WILENKO: Biochemische Zeitschrift, 1912, xlii, p. 58.

[2] WILENKO: Archiv für experimentelle Pathologie und Pharmakologie, 1913, lxxi, p. 266.

[3] LUSK: Proceedings of the Society for Experimental Biology and Medicine, 1914, xi, p. 49.

The amount of adrenalin injected to produce adrenalin glycosuria is enormous. Mr. H. Osgood has studied in this laboratory the effects on blood pressure of alternately stimulating the left splanchnic nerve (with the splanchnic vascular area eliminated) and injecting adrenalin, and by this method[1] has shown that the amount secreted after five seconds of stimulation varies between 0.0015 and 0.007 mgm. If 0.005 mgm. is taken as rather high average figure, and doubled (for the two glands), the amount would be 0.01 mgm. To produce adrenalin glycosuria an animal weighing 2 kilos would be injected with two hundred times this amount. It is granted that more adrenalin would be secreted if the nerves were stimulated longer than five seconds, and that with subcutaneous or intraperitoneal injection (to produce glycosuria), the amount of adrenalin in the blood at one time would not be so great as if the injection were intravenous; but even with these concessions the amount of adrenalin in the blood needed to produce glycosuria is probably much above the amount following physiological stimulation of the glands.

Other evidence that the amount of adrenalin discharged when the glands are stimulated is not so great as the amount needed to produce glycosuria when acting alone is presented in experiments by Macleod. He found that if the nerve fibres to the liver were destroyed, stimulation of the splanchnic, which would cause increased adrenal secretion, did not increase the blood sugar. The hyperglycaemia due to splanchnic stimulation, therefore, is a nervous effect, dependent, to be sure, on the presence of adrenalin in the blood, but the amount of adrenalin present is not in itself capable of evoking the hyperglycaemia.[2]

Furthermore, the hyperglycaemia following splanchnic stimulation may long outlast the stimulation period. The adrenals, however, as has been demonstrated by Osgood in this laboratory, are soon fatigued, and fail to respond to repeated stimulation. They seem to be incapable of prolonged action.

Again, as Macleod has shown, hyperglycaemia can be induced, if the adrenals are intact, merely by stimulating the nerves going to the liver.[3] The hyperglycaemia of splanchnic origin, therefore,

[1] *See* ELLIOTT: Journal of physiology, 1912, xliv, p. 376.

[2] MACLEOD: Diabetes, etc., pp. 64–73. [3] MACLEOD: Diabetes, etc., pp. 68–72.

is not due to a disturbance of the *use* of sugar in the body, as Wilenko claims for the hyperglycaemia after adrenalin injection, but is a result of a hyperglycogenolysis of nervous origin.

We may conclude therefore that since the conditions of Wilenko's observations are not comparable with emotional conditions, his inferences are not pertinent to the present discussion; that when both adrenalin and sugar are increased in the blood as a result of excitement, the hyperglycaemia is not due to adrenalin inhibiting the use of sugar by the tissues, and that there is no evidence at present to show that the brief augmentation of adrenal discharge, following excitement or splanchnic stimulation, affects in any deleterious manner the utilization of sugar as a source of energy. Indeed, the observation of Wilenko and of Patterson and Starling, above mentioned, that adrenalin increases the use of sugar by the heart, may signify that a physiological discharge of the adrenals can have a favorable rather than an unfavorable effect on the employment of sugar by the tissues.

The Vascular Changes Produced by Adrenalin are Favorable to Great Muscular Exertion

Quite in harmony with the foregoing argument that sugar and adrenalin, which are poured into the blood during emotional excitement, render the organism more efficient in the physical struggle for existence, are the vascular changes wrought by increased adrenalin, probably in co-operation with sympathetic innervations. Through oncometric studies, Oliver and Schäfer proved that the viscera of the splanchnic area — as the spleen, the kidneys and the intestines — suffer a considerable diminution of volume when adrenalin is administered, whereas the limbs into which the blood is forced from the splanchnic region actually increase in size.[1] In other words, at times of stress blood may be driven out of vegetative organs of the interior, which serve the routine needs of the body, into the skeletal muscles, which have to meet by extra action the urgent demands of conflict.

But there are exceptions to the statement that by adrenalin the viscera are emptied of their blood. It is well known that adrenalin

[1] Oliver and Schäfer: Journal of physiology, 1895, xviii, p. 240.

has a vasodilator, not a vasoconstrictor, effect on the arteries of the heart; it is well known also that adrenalin affects the intracranial and the pulmonary vessels only slightly, if at all.[1]

Thus the absolutely essential organs — the "tripod of life" — the heart, lungs and brain (as well as the skeletal muscles) — are, in times of excitement, when the adrenal glands discharge, abundantly supplied with blood taken from organs of less importance in critical moments.

The Muscles May Help Themselves by Operating the Adrenal Mechanism

As previously stated, Hoskins and I have shown that asphyxia causes an augmented secretion of adrenalin.[2] Asphyxia is a long recognized method of inducing hyperglycaemia. Hoskins and McClure, in extension of the theory which has underlain the researches summarized in this paper, have suggested that excessive muscular activity, such as might attend flight or conflict, would lead to partial asphyxia, and that this condition would naturally act in conjunction with emotional excitement and pain to bring forth a still greater adrenal discharge and a still greater output of sugar from the liver. And these in turn would serve the laboring muscles in the manner already described.[3] This suggestion is in accord with Macleod's that the increased glycogenolysis produced by muscular exercise is possibly associated with increased carbon dioxide in the blood.[4] And it also harmonizes with Zuntz's statement that the asphyxia of great physical exertion may call out sugar to such a degree that, in spite of the increased use of it in the active muscles, glycosuria may ensue.[5]

Conclusion

To what extent the slight constant secretion of the adrenal glands serves the organism is not yet well determined. As several observers have shown, the first effect of injecting small amounts

[1] *See* BIEDL: *Loc. cit.*, pp. 434, 435.
[2] CANNON and HOSKINS: *Loc. cit.*, p. 275.
[3] HOSKINS and MCCLURE: Archives of internal medicine, 1912, x, p. 355.
[4] MACLEOD: Diabetes, etc., p. 184. [5] ZUNTZ: *Loc. cit.*, p. 854.

of adrenalin into carnivorous animals is to lower blood pressure.[1] Adrenal secretion cannot be, therefore, at least among the carnivora, a direct factor in maintaining the normal high tonus of the vasomotor system. It is probable, however, that incredibly minute amounts of this substance in the circulating blood somehow sensitize the myoneural junctions of the sympathetic system, and thus aid the nervous action.[2] Such quiet service, however, is quite distinct from the profound changes in the organism which larger amounts of adrenalin are capable of provoking or helping to provoke.

The cessation of activities of the alimentary canal (thus freeing energy for other parts); the shifting of the blood from the less insistent abdominal viscera to the organs immediately essential to life itself, such as the lungs, the heart, the central nervous system and, at critical moments, the skeletal muscles as well; the increased cardiac vigor; the quick abolition of the effects of muscular fatigue, the mobilizing of energy-giving sugar in the circulation — these are the changes which occur when fear or rage or pain causes the adrenal glands to pour forth an excessive secretion. These changes in the body are, each one of them, *directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve;* for fear and rage are organic preparations for action, and pain is the most powerful known stimulus to supreme exertion. The organism which with the aid of increased adrenal secretion can best muster its energies, can best call forth sugar to supply the laboring muscles, can best lessen fatigue, and can best send blood to the parts essential in the run or the fight for life, is most likely to survive. Such, according to the view here propounded, is the function of the adrenal medulla at times of great emergency.[3]

[1] *See* HOSKINS and MCCLURE: *Loc. cit.*, p. 353. CANNON and LYMAN: *Loc. cit.* p. 376. [2] *Cf.* ELLIOTT: Journal of physiology, 1904, xxxi, p. xx.

[3] Since this paper was prepared Dr. W. L. Mendenhall and I have found that splanchnic stimulation may greatly hasten the coagulation of the blood. This result does not occur if the adrenal gland has been removed on the side stimulated. Thus excitement and pain, through the agency of the adrenal medulla, may be serviceable to the organism in preventing loss of blood in case of vascular injury. The pertinence of these observations to the view presented in this paper is obvious.